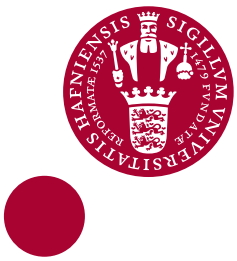


Current state of knowledge on biological effects from contaminants on arctic wildlife and fish

Dietz, Rune; Letcher, Robert J.; Desforges, Jean-Pierre; Eulaers, Igor; Sonne, Christian; Wilson, Simon; Andersen-Ranberg, Emilie; Basu, Niladri; Barst, Benjamin D.; Bustnes, Jan Ove; Bytingsvik, Jenny; Ciesielski, Tomasz M.; Drevnick, Paul E.; Gabrielsen, Geirw.; Haarr, Ane; Hylland, Ketil; Jenssen, Bjorn Munro; Levin, Milton; McKinney, Melissa A.; Norregaard, Rasmus Dyrmose; Pedersen, Kathrine E.; Provencher, Jennifer; Styrishave, Bjarne; Tartu, Sabrina; Aars, Jon; Ackerman, Joshua T.; Rosing-Asvid, Aqqalu; Barrett, Rob; Bignert, Anders; Borns, Erik W.; Branigan, Marsha; Braune, Birgit; Bryan, Colleen E.; Dam, Maria; Eagles-Smith, Collin A.; Evans, Marlene; Evans, Thomas J.; Fisk, Aaron T.; Gamberg, Mary; Gustavson, Kim; Hartman, C. Alex; Helander, Bjorn; Herzog, Mark P.; Hoekstra, Paul F.; Houde, Magali; Hoydal, Katrin; Jackson, Allyson K.; Kucklick, John; Lie, Elisabeth; Loseto, Lisa; Mallory, Mark L.; Miljeteig, Cecilie; Mosbech, Anders; Muir, Derek C. G.; Nielsen, Sanna Tuni; Peacock, Elizabeth; Pedro, Sara; Peterson, Sarah H.; Polder, Anuschka; Riget, Frank F.; Roach, Pat; Saunes, Halvor; Sinding, Mikkel-Holger S.; Skaare, Janneche U.; Sondergaard, Jens; Stenson, Garry; Stern, Gary; Treu, Gabriele; Schuur, Stacy S.; Vikingsson, Gisli

Published in:
Science of the Total Environment

DOI:
10.1016/j.scitotenv.2019.133792

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Science of the Total Environment 696 (2019) 133792

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Current state of knowledge on biological effects from contaminants on arctic wildlife and fish

Rune Dietz [a,*], Robert J. Letcher [b,*], Jean-Pierre Desforges [a], Igor Eulaers [a], Christian Sonne [a], Simon Wilson [c], Emilie Andersen-Ranberg [a], Niladri Basu [d], Benjamin D. Barst [d], Jan Ove Bustnes [e], Jenny Bytingsvik [f,g], Tomasz M. Ciesielski [h,i], Paul E. Drevnick [j,k], Geir W. Gabrielsen [l], Ane Haarr [m], Ketil Hylland [m], Bjørn Munro Jenssen [a,h,i], Milton Levin [n], Melissa A. McKinney [d], Rasmus Dyrmose Nørregaard [a], Kathrine E. Pedersen [o], Jennifer Provencher [p], Bjarne Styrishave [q], Sabrina Tartu [l], Jon Aars [l], Joshua T. Ackerman [r], Aqqalu Rosing-Asvid [s], Rob Barrett [t], Anders Bignert [u], Erik W. Born [s], Marsha Branigan [v], Birgit Braune [b], Colleen E. Bryan [w], Maria Dam [x], Collin A. Eagles-Smith [y], Marlene Evans [z], Thomas J. Evans [aa], Aaron T. Fisk [ab], Mary Gamberg [ac], Kim Gustavson [a], C. Alex Hartman [r], Björn Helander [ad], Mark P. Herzog [r], Paul F. Hoekstra [ae], Magali Houde [af], Katrin Hoydal [x], Allyson K. Jackson [ag], John Kucklick [w], Elisabeth Lie [ah], Lisa Loseto [ai], Mark L. Mallory [aj], Cecilie Miljeteig [c], Anders Mosbech [a], Derek C.G. Muir [ak], Sanna Túni Nielsen [y], Elizabeth Peacock [al,am], Sara Pedro [d], Sarah H. Peterson [r], Anuschka Polder [an], Frank F. Rigét [a], Pat Roach [ao], Halvor Saunes [ap], Mikkel-Holger S. Sinding [t,aq], Janneche U. Skaare [ar], Jens Søndergaard [a], Garry Stenson [as], Gary Stern [at], Gabriele Treu [au], Stacy S. Schuur [w], Gísli Víkingsson [av]

[a] Aarhus University, Arctic Research Centre (ARC), Department of Bioscience, Frederiksborgvej 399, P.O. Box 358, DK-4000 Roskilde, Denmark
[b] Eecotoxicology and Wildlife Health Division, Science and Technology Branch, Environment and Climate Change Canada, 1125 Colone By Dr., Carleton University, Ottawa, ON K1A 0H3, Canada
[c] Arctic Monitoring and Assessment Programme (AMAP) Secretariat, Fram Centre, P.O. Box 6606 Langnes, N-9296 Tromsø, Norway
[d] Faculty of Agricultural and Environmental Sciences, McGill University, Montréal, Sainte-Anne-de-Bellevue, Quebec H9X 3V9,Canada
[e] Norwegian Institute for Nature Research, Unit for Arctic Ecology, Fram Centre, NO-9296 Tromso, Norway
[f] Akvaplan-niva AS, Fram Centre, High North Research Centre for Climate and the Environment, Hjalmar Johansens Gate 14, 9007 Tromsø, Norway
[g] Fram Centre and Norwegian Polar Institute, Tromsø NO-9296, Norway
[h] Department of Biology, Norwegian University of Science and Technology, NO-7491 Trondheim, Norway
[i] Department of Arctic Technology, University Centre in Svalbard, NO-9171 Longyearbyen, Norway
[j] Alberta Environment and Parks, Environmental Monitoring and Science Division, 3535 Research Road NW, University Research Park, Calgary AB T2L 2K8, Canada
[k] University of Michigan, School for Environment and Sustainability, 440 Church St., Ann Arbor, MI 48109, USA
[l] Norwegian Polar Institute, Fram Centre, NO-9296 Tromsø, Norway
[m] Department of Biosciences, University of Oslo, P.O Box 1066 Blindern, 0316 Oslo, Norway
[n] Department of Pathobiology and Veterinary Science, University of Connecticut, 61 North Eagleville Road, Unit 3089, Storrs, CT 06269-3089, USA
[o] University of Copenhagen, Department of Plant and Environmental Sciences, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark
[p] Department of Biology, Acadia University, Wolfville, Nova Scotia B4P 2R6, Canada.
[q] Toxicology Laboratory, Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark
[r] U.S. Geological Survey, Western Ecological Research Center, Dixon Field Station, 800 Business Park Drive, Suite D, Dixon, California 95620, USA
[s] Greenland Institute of Natural Resources, P.O. Box 570, DK-3900 Nuuk, Greenland
[t] Tromsø University Museum, Tromsø, NO-9037 Tromsø, Norway
[u] Dep. of Environmental Research and Monitoring, Swedish Museum of Natural History, PO Box 50 007, S-104 05 Stockholm, Sweden
[v] Department of Environment and Natural Resources, Government of the Northwest Territories, P.O. Box 2749, Shell Lake, Inuvik X0E 0T0, NT, Canada
[w] National Institute of Standards and Technology, Chemical Sciences Division, Hollings Marine Laboratory, 331 Fort Johnson Road, Charleston, SC 29412, USA
[x] Environment Agency, Traðagøta 38, P.O. Box 2048, FO-165 Argir, Faroe Islands
[y] U.S. Geological Survey, Forest and Rangeland Ecosystem Science Center, 3200 SW Jefferson Way, Corvallis, Oregon 97331, USA
[z] Aquatic Ecosystem Protection Research Division, Environment Canada, 11 Innovation Blvd, Saskatoon, SK S7N 3H5, Canada
[aa] U.S. Fish and Wildlife Service, Office of Subsistence Management, 1011 E. Tudor Rd., MS-121, Anchorage, AK 99503, USA
[ab] Great Lakes Institute for Environmental Research, University of Windsor, 401 Sunset Ave, Windsor, ON N9B 3P4, Canada
[ac] Gamberg Consulting, Box 30130, Whitehorse, Yukon Y1A 5M2, Canada
[ad] Environmental Research & Monitoring, Swedish Museum of Natural History, Frescativägen 40, PO Box 50007, 104 05 Stockholm, Sweden
[ae] Syngenta Canada Inc., 140 Research Ln, Guelph, ON N1G 4Z3, Canada
[af] Environment and Climate Change Canada, Montreal, QC H2Y 2E7, Canada
[ag] Oregon State University, Department of Fisheries and Wildlife, 104 Nash Hall, Corvallis, OR 97331, USA
[ah] NIVA, Gaustadalléen 21, 0349 Oslo, Norway

* Corresponding authors.
E-mail addresses: rdi@bios.au.dk (R. Dietz), robert.letcher@canada.ca (R.J. Letcher).

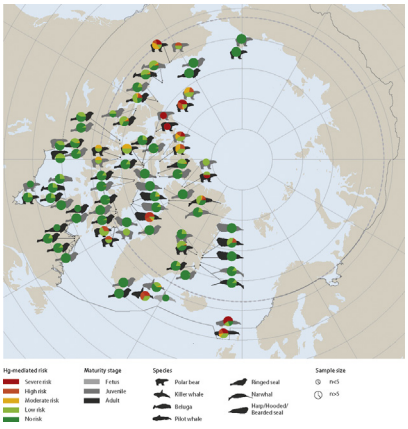
https://doi.org/10.1016/j.scitotenv.2019.133792

[ai] Freshwater Institute, Fisheries and Oceans Canada, 501 University Cres., Winnipeg, MB R3T 2N6, Canada
[aj] Coastal Wetland Ecosystems, Biology Department, Acadia University, 15 University Drive, Wolfville, Nova Scotia B4P 2R6, Canada
[ak] Environment and Climate Change Canada, Aquatic Contaminants Research Division, 867 Lakeshore Road, Burlington L7S 1A1, Ontario, Canada
[al] Alaska Science Center, US Geological Survey, 4210 University Drive, Anchorage, AK 99508, United States
[am] Department of Environment, Government of Nunavut, Igloolik, Nunavut, Canada
[an] Department of Food Safety and Infection Biology, Norwegian University of Life Sciences, P.O. Box 8146 Dep, N-0033 Oslo, Norway
[ao] Aboriginal Affairs and Northern Development Canada, 415C-300 Main Street, Whitehorse, YT Y1A 2B5, Canada
[ap] COWI Norge, Karvesvingen 2, 0579 Oslo, Norway
[aq] Centre for Geogenetics, Natural History Museum of Denmark ('Geologisk Museum'), Øster Voldgade 5-7, DK-1350 Copenhagen K, Denmark
[ar] National Veterinary Institute, P.O. Box 8156 dep., N-0033 Oslo, Norway
[as] Northwest Atlantic Fisheries Centre, 80 East White Hills vie, Newfoundland and Labrador, St John's A1C 5X1, Department DFO-MPO, Canada
[at] Centre for Earth Observation Sciences (CEOS), Clayton H. Riddell Faculty of Environment, Earth and Resources, University of Manitoba, 586 Wallace Bld, 125 Dysart Rd., Winnipeg, Manitoba R3T 2N2, Canada
[au] Leibniz Institute for Zoo and Wildlife Research, Alfred-Kowalke-Str. 17, 10315 Berlin, Germany
[av] Marine and Freshwater Research Institute, Skúlagata 4, 101Reykjavík, Iceland

HIGHLIGHTS

- We review current knowledge of contaminant exposure and effects in Arctic biota.
- Effects were found on vitamin metabolism, immune functioning and hormones.
- Other effects included oxidative stress, pathology and reproduction.
- Marine mammals and seabirds well studied, terrestrial wildlife and fish much less.
- Methods exist to model contaminant population effects, but more work is needed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 13 May 2019
Received in revised form 19 July 2019
Accepted 4 August 2019
Available online 13 August 2019

Editor: Adrian Covaci

Keywords:
Biological effects
Circumpolar Arctic
Fish
Mercury
Organohalogen compounds
Wildlife

ABSTRACT

Since the last Arctic Monitoring and Assessment Programme (AMAP) effort to review biological effects of the exposure to organohalogen compounds (OHCs) in Arctic biota, there has been a considerable number of new Arctic effect studies. Here, we provide an update on the state of the knowledge of OHC, and also include mercury, exposure and/or associated effects in key Arctic marine and terrestrial mammal and bird species as well as in fish by reviewing the literature published since the last AMAP assessment in 2010. We aimed at updating the knowledge of how single but also combined health effects are or can be associated to the exposure to single compounds or mixtures of OHCs. We also focussed on assessing both potential individual as well as population health impacts using population-specific exposure data post 2000. We have identified quantifiable effects on vitamin metabolism, immune functioning, thyroid and steroid hormone balances, oxidative stress, tissue pathology, and reproduction. As with the previous assessment, a wealth of documentation is available for biological effects in marine mammals and seabirds, and sentinel species such as the sledge dog and Arctic fox, but information for terrestrial vertebrates and fish remain scarce. While hormones and vitamins are thoroughly studied, oxidative stress, immunotoxic and reproductive effects need further investigation. Depending on the species and population, some OHCs and mercury tissue contaminant burdens post 2000 were observed to be high enough to exceed putative risk threshold levels that have been previously estimated for non-target species or populations outside the Arctic. In this assessment, we made use of risk quotient calculations to summarize the cumulative effects of different OHC classes and mercury for which critical body burdens can be estimated for wildlife across the Arctic. As our ultimate goal is to better predict or estimate the effects of OHCs and mercury in Arctic wildlife at the individual, population and ecosystem level, there remain numerous knowledge gaps on the biological effects of exposure in Arctic biota. These knowledge gaps include the establishment of concentration thresholds for individual compounds as well as for realistic cocktail mixtures that in fact indicate biologically relevant, and not statistically determined, health effects for specific species and subpopulations. Finally, we provide future perspectives on understanding Arctic wildlife health using new in vivo, in vitro, and in silico techniques, and provide case studies on multiple stressors to show that future assessments would benefit from significant efforts to integrate human health, wildlife ecology and retrospective and forecasting aspects into assessing the biological effects of OHC and mercury exposure in Arctic wildlife and fish.

Contents

1. Introduction

Within the circumpolar Arctic there has been minimal direct production and use of industrial contaminants like persistent organic pollutants (POPs) and mercury (Hg). However, POPs, or their precursors, degradation products and metabolites, are carried into the Arctic from more southerly latitudes via long-range atmospheric transport as well as via ocean currents and rivers (Braune et al., 2005; de Wit et al., 2006, 2010). As a result, lipophilic contaminants, such as POPs and methylmercury (MeHg) bioaccumulate in Arctic organisms and biomagnify through Arctic marine food webs, generating concern for the health of exposed wildlife and for indigenous populations that consume these food items as part of a traditional diet.

The harmful effects of many POPs, largely comprised of chlorinated, brominated and/or fluorinated organohalogenated compounds (OHCs), on human and environmental health have been long recognized. In 2001, under a groundbreaking United Nations treaty – the Stockholm Convention – signatory countries agreed to reduce or eliminate the production, use, and/or release of 12 key POPs; the so-called ‘dirty dozen’(Kaiser and Enserink, 2000) and in 2017 a similar treaty for mercury (the Minamata Convention on Mercury) entered into force worldwide (Evers et al., 2016). During the past two decades, the concentrations of many of these legacy POPs in Arctic marine biota have declined, although for the last ten years or so concentrations of polychlorinated biphenyls (PCBs) and chlordanes have remained relatively constant and at high levels in wildlife tissues (AMAP, 2016). Further, every year thousands of new synthetic chemicals are produced, and recently there have been reports of chemicals of emerging concern (CECs) in humans and marine biota, for example, flame retardants (FRs) including polybrominated diphenyl ethers (PBDEs) (Vorkamp et al., 2019) among many others (AMAP, 2017). The current state-of-knowledge of CECs in the Arctic is detailed in a companion assessment

(AMAP, 2017) and associated journal review papers on FRs (Vorkamp et al., 2019) and per-/poly-fluoroalkyl substances (PFASs; Muir et al., 2019). Many of the CECs that have been reported in Arctic wildlife and fish are generally present at much lower tissue levels than for legacy POPs such as PCBs, organochlorine pesticides (OCPs), and PBDEs.

Among the eight Arctic countries collaborating on Arctic pollution issues within the Arctic Monitoring and Assessment Programme (AMAP; Canada, Denmark/Greenland/Faroes Islands, Finland, Iceland, Norway, Russia, Sweden, USA), most effect studies on wildlife and fish were historically available from the North Atlantic between Greenland and Svalbard (Norway) where tissue concentrations of OHCs and other POPs have been shown to be highest. This was consistently emphasized in the previous three rounds of AMAP reports on POPs and metals (AMAP, 1998, 2004, 2016; Letcher et al., 2010; Dietz et al., 2013a). The last AMAP report on POP effects that focused on OHCs (Letcher et al., 2010) gave a detailed review of all health effect categories available at that time for all species of Arctic wildlife and fish. The latest Hg assessments (Dietz et al., 2013a; Outridge et al., 2011a, 2011b) gave similar insights specific to Hg, including transport, geographical trends, links to climate change, and human health.

For the period 1998–2012, there were far fewer studies of POP and metal levels and any observed effects in Arctic fish than there were for top predators such as polar bear (*Ursus maritimus*) and glaucous gull (*Larus hyperboreus*). However, this has now changed, and as of 2017 there have been many effect studies reported or currently underway in fish and other Arctic wildlife, including the measurement of strategic biomarker endpoints, in vitro experiments for top predator species, and pathological studies on fish around Arctic mining sites. Nevertheless, for wildlife and fish species endemic to the Arctic, it should be noted that there are also numerous natural (ecological and physiological) and anthropogenic factors, including climate change, invasive species and pathogens, changes in food web dynamics and predator-prey interactions, that can influence and confound the exposure to and effects of contaminants (Macdonald et al., 2003, 2005; UNEP/AMAP, 2011; Jenssen et al., 2015; McKinney et al., 2015).

The present assessment does not address temporal trends as Rigét et al. (2019) recently reported updated time trends of OHCs in biota from the Arctic region. In general, the reported legacy POPs showed decreasing concentrations over the last two to three decades. Few time-series of legacy POPs showed increasing trends and only at sites suspected to be influenced by local source. The brominated flame retardant congener BDE-47 and perfluorooctane sulfonic acid (PFOS) showed increasing concentration up to approximately the mid-2000s followed by a decreasing concentration. Hexabromocyclododecane (HBCDD) was the only compound in the study of Rigét et al. (2019) showing a consistent increasing trend. Only 12% of the long-term time-series were able to detect a 5% annual change with a statistical power of 80% at $\alpha = 0.05$. The remaining 88% of time series need additional years of data collection before fulfilling these statistical requirements. In the case of the organochlorine long-term time-series, 45% of these would require >20 years monitoring before this requirement could be fulfilled.

The aim of the present assessment is to summarize the current state of knowledge and understanding of legacy pollutants and chemicals of emerging Arctic concern and associated biological effects in Arctic wildlife and fish. This work stems from the Arctic Monitoring and Assessment Programme (AMAP), which is tasked with monitoring and reporting pollution issues in the circumpolar Arctic, however with limited information from the Russian Federation (Fig. 1). The last relevant AMAP reports focused on reviewing detailed POP and Hg health effects studied up to approximately 2010 (Letcher et al., 2010; Dietz et al., 2013a; Outridge et al., 2011a, 2011b). Here we review the literature on the biological effects of a broad range of contaminant in the Arctic published since 2010, providing for the first time a combined risk assessment for OHCs and Hg which act via similar modes and mechanisms. We explicitly address important knowledge gaps identified in previous AMAP reports regarding complex contaminant mixtures and effects at the individual and population-level. We use contaminant levels in Arctic species for a circumpolar We use contaminant levels in Arctic species for a circumpolar risk quotient analysis, enabling the estimation of the cumulative effects of environmental contaminant mixtures as well as spatial risk assessment at the population-level.

2. Biological effects of contaminant exposure in Arctic wildlife and fish

2.1. Marine and terrestrial mammals

2.1.1. Vitamins and oxidative stress

Vitamins A, D and E are essential nutrients and act as *endo-* or *exo-*hormones, involved in growth, development, reproduction, bone mineral homeostasis, protection against tissue damage, and immune and endocrine function (Blomhoff, 1994; Debier and Larondelle, 2005). The group of fat-soluble vitamin A compounds includes, most notably, retinol, retinyl esters and retinoic acid. Vitamin E refers collectively to several forms of tocopherols and tocotrienols, and these are the most abundant antioxidants in vertebrates. Vitamin D is both endogenously and exogenously acquired, and its metabolism in several organs results in the formation of active metabolites (e.g., 25-hydroxycholecalciferol or calcifediol), which control the homeostasis of calcium, phosphate and other nutrients. Because of their physiological importance, changes in these vitamins are considered as biomarkers of OHC exposure and effects in wildlife. Multiple studies on both free-ranging and captive experimental terrestrial and marine mammals in the Arctic have been published since the previous AMAP assessment (Letcher et al., 2010), linking tissue contaminant burdens to circulating and tissue residues of vitamins (Supplemental Information Table 1).

In aa study of 66 beluga (*Delphinapterus leucas*) in western Arctic Canada (Beaufort Sea), Desforges et al. (2013) measured tissue levels of vitamins A and E as well as blubber OHC concentrations. Despite the confounding influence of biological factors (including age, condition and diet) on vitamin physiology, contaminant exposure was found to be significantly related to tissue vitamin concentrations; hepatic vitamin levels were negatively correlated with the sum of polychlorinated biphenyl (ΣPCB) concentrations (3093 ± 209 ng/g lipid weight (lw)), while plasma and blubber vitamin levels increased with ΣPCB concentrations. From these results the authors calculated an integrated toxicity reference value of a 1.6 μg/g lw ΣPCB concentration threshold for vitamin A and E disruption in beluga.

Hoydal et al. (2016) reported on blood plasma and liver concentrations of OHCs in relation to vitamin biomarkers in pilot whales (*Globicephala melas*) from the Faroe Islands (SI Table 1). Faroese pilot whales had high body burdens of OHCs such as PCBs, organochlorine pesticides (OCPs) and BFRs. Multivariate statistical modelling showed that age and sex influenced the relationship between vitamin biomarkers and OHC concentrations. In plasma of juvenile whales, α–tocopherol was also positively correlated with all detected OHCs, though only a few significant correlations were found between single OHCs and retinol and vitamin D in plasma. There were significant negative relationships between hepatic polybrominated diphenyl ether (PBDE) concentrations and retinol (only for BDE47) and γ–tocopherol (only for BDE49, BDE47, BDE99, BDE100, and BDE153) in liver. The authors concluded that the relationships between OHCs and vitamins suggest that OHCs seem to have only minor effects on vitamin concentrations in Faroese pilot whales.

Tissue levels of vitamins A and D as well as mRNA expression of vitamin A receptors were compared between ringed seals (*Pusa hispida*) from the heavily polluted Baltic Sea and the relatively unpolluted Svalbard region (Routti et al., 2010a). Baltic seals were found to have lower plasma retinol but higher hepatic gene expression of retinoic acid receptor alpha (RARα), while no differences were found in hepatic vitamin A levels. Baltic seals also had higher plasma calcitriol (vitamin D) than the

Fig. 1. Regions from which contaminant exposure and effect studies were available for the present assessment.

Svalbard seals. Since the reverse trend in calcitriol and significant differences in hepatic vitamin A levels were noted in earlier studies of these populations in the 1990s (Nyman et al., 2003; Routti et al., 2008), the authors suggested that plasma calcitriol and hepatic vitamin A concentrations are no longer depressed due to contaminant exposure in Baltic ringed seals, probably arising from significantly reduced contaminant levels in Baltic ringed seals between 2002 and 2007.

Similarly, Kanerva et al. (2012) compared ringed seals from the Baltic Sea and Svalbard in terms of differences in antioxidants and oxidative stress. To study the possible effects of the temporal decrease in the levels of OHCs in the Baltic seals, the samples originated from two different periods: 1996–1997 and 2002–2007. The results showed that glutathione metabolism was enhanced in the Baltic seals compared to those from Svalbard. However, no signs of oxidative damage were found in either seal population. Seals have evolved high antioxidant capacity as adaptations to prolonged fasting, sleep apnoea and hypoxemia, and ischemia/reperfusion which are normally associated with increased systemic or local oxidative damage in mammals (Vazquez-Medina et al., 2012). Thus, the authors suggested that the similarities in oxidative stress levels despite the differences in antioxidant responses between the two populations could be due to a high evolutionary capacity to increase antioxidant defense in seals, and thus a high resistance to oxidative stress.

Contaminants importantly, were from regions bordering the Arctic, results were available from grey seals (*Halichoerus grypus*) from the Isle of May, Scotland during the breeding season in November–

December 2008 for contaminant effects on vitamin A (van den BergheHere concentrations of ΣPCBs, ΣPBDEs, and several individual PCB congeners in female seals were positively correlated with vitamin A concentrations in serum and inner blubber. Similar to the results from Beaufort belugas, it was concluded that contaminants may act via mobilization of hepatic retinoid stores and redistribution in the blubber, a storage site for vitamin A in marine mammals. Furthermore, there was a tendency for a positive relationship between serum concentrations of ΣPCBs and the PCB metabolite 4-hydroxy (OH)-CB-107 with serum vitamin A. Importantly, some of the grey seals in the study were lactating mothers, a factor which surely confounded both vitamin and contaminant dynamics. For instance, Routti et al. (2010b) described higher concentrations of plasma and hepatic persistent organic pollutants (POP) and vitamin A levels in molting ringed seals indicating seasonal variations. Together, these studies underline the importance of considering life-history and physiological state as confounding factors when studying possible effects of POPs on vitamin status in marine mammals.

In Baikal seals, exposure to OHCs was fond to induce production and increased activities of cytochrome P450 (CYP) enzymes, a potential marker of oxidative stress (Hirakawa et al., 2011). In animals sampled in summer 1992 and again in 2005, chronic exposure to polychlorinated-dibenzo-*p*-dioxins and related dioxin-like compounds were related to oxidative stress induction. The expression levels of CYP1A2 were positively correlated with levels of malondialdehyde, a biomarker of lipid peroxidation, and of etheno-dA, a DNA adduct. Thus, in seals OHC exposure may cause enhanced lipid peroxidation through the production of reactive oxygen species triggered by CYP1A2 induction. Furthermore, there was a positive relationship between malondialdehyde concentrations and heme oxygenase activities, suggesting heme degradation by reactive oxygen species. The responses reported for other biomarkers of inflammation, indicated that the increased oxidative stress caused by the induction of CYP1 isoenzymes resulted in increased inflammation. In another study on Baikal seals sampled in summer 2005, hepatic expression levels of CYP1 genes were positively correlated with the concentrations of OH-PCBs, compounds known to induce oxidative stress (Nomiyama et al., 2014). This indicates that these OH-PCB metabolites may play an important role in inducing oxidative stress in seals.

In a study on 166 polar bears from East Greenland sampled between 1994 and 2008, hepatic, renal and whole blood vitamin A and E were measured and compared with a suite of OHCs (Bechshøft et al., 2016). In liver, vitamin A levels were positively correlated with ΣPCB, but negatively correlated with ΣPBDE, ΣDDT, and hexachlorocyclohexane (ΣHCH) concentrations, while no relationships were observed for vitamin E. Kidney cortex vitamin A and E levels correlated negatively with ΣDDTs, ΣPBDEs and/or chlordanes (ΣCHLs), while vitamin E levels also correlated positively with ΣMirex. Lastly, vitamin A concentrations correlated negatively with many levels of OHCs in whole blood and no significant correlations were reported for vitamin E. The varied directionality of effects with different OHCs is difficult to interpret in a mechanistic way, but perhaps suggest that these complex contaminant mixtures are interfering with homeostatic processes. This study also reported increased contaminant concentrations during the study period, in accordance with a reported dietary shift towards more contaminated harp seal (*Pagophilus groenlandicus*) and hooded seal (*Cystophora cristata*) (Dietz et al., 2013a, 2013b; McKinney et al., 2013). These results also underline the potential confounding effects of temporal dietary shifts and changing contaminant exposure when evaluating the presence of a true contaminant effect.

In a controlled study where exposed Greenland sledge dogs (*Canis familiaris*) were given a diet containing minke whale (*Balaenoptera acuterostrata*) blubber 'naturally' contaminated with POPs (dog ΣOHCs = 5.0 μg/g lw) and a reference group consumed uncontaminated pork fat (dog ΣOHCs = 0.09 μg/g lw), hepatic retinol concentrations were negatively associated with those of ΣDDTs and ΣPBDEs (Kirkegaard et al., 2010). Hepatic vitamin E (tocopherol) levels were lower in exposed dogs compared to control dogs, whereas no difference in vitamin A was observed for the exposed group. Kidney retinol levels were positively correlated with ΣCHL and dieldrin concentrations, while kidney tocopherol was negatively correlated with ΣPCBs. The authors concluded even at low exposure levels, OHCs appear to be affecting physiological vitamin levels. However, in another study using domesticated Arctic foxes (*Vulpes lagopus*) fed the same minke whale blubber or pork fat diet, there were no observed differences in plasma retinol or tocopherol between feeding groups (Hallanger et al., 2012), highlight a clear species difference in susceptibility to exposure and effect.

The same sledge dog cohort was also used to examine the status of vitamin D in mothers and their pups (Sonne et al., 2014a). The study showed that in the exposed mothers, the hepatic concentration of 25-OH vitamin D-3 (25OHD3) was significantly lower than in the control mothers. No between-group differences were identified for hepatic vitamin D3 or plasma 25OHD3 concentrations in mothers. However, hepatic D3 and plasma 25OHD3 concentrations were significantly higher in the exposed pups compared to the control pups. When the results from both mothers and pups were pooled, a significant negative relationship between adipose tissue concentration of ΣPCBs and plasma 25OHD3 concentrations was identified, and a similar trend was found for hepatic 25OHD3 versus adipose ΣPCBs. Due to differences in dietary composition of the food provided to the two groups, the results indicated that the homeostasis and metabolism of vitamin D compounds may respond differently to the dietary composition of fatty acids and OHC exposure. Ultimately, the authors could not confirm whether the lower level of 25OHD3 in the liver of exposed dogs would have had any negative effects on immunity and reproduction.

2.1.2. Endocrinology

According to Jenssen (2006) the effects of global climate change on biodiversity and ecosystem function encompass multiple complex dynamic processes. Climate change and exposure to endocrine-disrupting chemicals are currently regarded as two of the most serious anthropogenic threats to biodiversity and ecosystems. This implies a need for attention to the possible effects of endocrine-disrupters on the ability of Arctic wildlife to adapt to environmental alterations caused by climate change. Relationships between POPs and hormones in Arctic wildlife imply that these chemicals pose a threat to the endocrine systems of these species. The strongest relationships have been reported for the thyroid hormone system, but effects are also seen in sex steroid hormones and cortisol (Letcher et al., 2010 and references therein). Although behavioral and morphological effects of POPs are consistent with endocrine disruption, no direct evidence exists for such a cause-effect relationship. Because endocrine systems are important for enabling animals to respond to environmental stress, endocrine-disrupting chemicals may interfere with adaptations to increased environmental stress (Letcher et al., 2010). This is likely to concern adaptive responses regulated by the thyroid, sex steroid, and glucocorticosteroid systems.

Thyroid hormones are an endpoint in studies of contaminant bioaccumulation as well as global climate change. Morphological and pathological changes in thyroid hormone balance can affect reproduction success, growth, thermoregulation and immune competence of neonatal and adult individuals, functions crucial for life in the Arctic (Zoeller et al., 2002; Grandjean and Landrigan, 2006; Klecha et al., 2008). The previous AMAP assessment report included several studies on the association between POP body burdens and circulating concentrations of thyroid hormones in marine mammals (Letcher et al., 2010). Since 2010, several new articles have been published regarding effects on thyroid hormones in marine mammals as well as mechanisms involved in thyroid disruption. New research is also available concerning experimental studies on the effects of POPs on thyroid and steroid hormones in Greenland sledge dogs (Kirkegaard et al., 2011; Sonne et al., 2014a, 2014b, 2016), domesticated Arctic foxes (Hallanger et al., 2012;

Helgason et al., 2013; Rogstad et al., 2017) (Sonne et al., 2010a, 2013a). endocrine-disrupting chemical-related studies have been reported for seals (Routti et al., 2010a; Wang et al., 2010; Gabrielsen et al., 2011; Villanger et al., 2013; Brown et al., 2014; Imaeda et al., 2014), toothed whales (Buckman et al., 2011; Das et al. 2006, Siebert et al., 2011, Villanger et al., 2011b, Schwacke et al., 2012; Noel et al., 2014) and polar bears (Bourgeon et al., 2017; Gutleb et al., 2010; Knott et al., 2011; Simon et al., 2011; Sonne et al., 2011; Villanger et al., 2011a; Bytingsvik et al., 2013; Gabrielsen et al., 2015; Bourgeon et al., 2017).

Thyroid hormone receptor beta (THRB) and deiodinase I hepatic gene expression levels were higher in ringed seals from the polluted Baltic Sea relative to ringed seals from the less-polluted waters around Svalbard (Routti et al., 2010a).) Free 3,3′,5-triiodothyronine (FT3) in plasma was also found to be higher in Baltic seals. Since vitamins were also reported in that study, the authors concluded that thyroid hormones were a more sensitive effect biomarker of POP exposure in ringed seals. Thyroid hormone status was evaluated in East Greenland hooded seals and OH-PCBs were found to be the major contaminant class of interest, showing negative correlations with free thyroxine FT4:FT3 and TT3:FT3 ratios in pups (Gabrielsen et al., 2011; Villanger et al., 2011a). In contrast, Brown et al. (2014) did not find any association of thyroid hormone receptor alpha (THRA) expression with ΣPCBs in ringed seals at a military radar site locally polluted with ΣPCBs on the Labrador coast of Arctic Canada. Similarly, POPs were not significant contributors to thyroid hormone status in Baikal seals (Imaeda et al., 2014).

For cetaceans, Buckman et al. (2011) found that ΣPCBs increased expression of the THRBTHRB gene in killer whales (*Orcinus orca*) from British Columbia, Canada, although this was not observed for beluga from the Beaufort Sea (Noel et al., 2014). A study on Svalbard beluga showed that concentrations of the known or suspected thyroid disruptive contaminants BDE28, BDE47, BDE99, BDE100, and BDE154, hexachlorobenzene (HCB), and CB105 were negatively correlated with circulating levels of total T4 (TT4), FT4 and FT3 (Villanger et al., 2011b). Hoydal et al. (2016) investigated pilot whales from the Faroe Islands and found significant positive relationships between OHCs and thyroid hormone concentrations in the youngest juveniles only. As with seals, the effects of contaminants on thyroid hormones appear population and species specific, and clear results are most likely confounded by various natural and anthropoenic factors.

Bourgeon et al. (2017) reported negative relationships between circulating TT3 and FT3 and concentrations of PCBs and OCPs in polar bears from the Barent Sea. Furthermore, FT3 concentrations decreased with increasing PFAS concentrations. The results of the study, conducted with a large number of individuals ($n = 112$), showed that the relationships were only found in spring and not in autumn. In southern Beaufort Sea polar bears, negative relationships were reported between PCBs and TT4, while TT3 was positively correlated with Hg (Knott et al., 2011). For pollutants in polar bears, it was shown that OH-PCBs (Gutleb et al., 2010; Simon et al., 2011; Bytingsvik et al., 2013) and branched nonylphenol (Simon et al., 2013) bind to transthyrethin in competition with thyroid hormones, and that these compounds may fully saturate the available transthyrethin. A study on East Greenland polar bears confirmed negative relationships between individual PCB congeners and their OH-PCB metabolites and T4 in both plasma and muscle (Gabrielsen et al., 2015). Furthermore, in general, PCBs, OH-PCBs and PBDEs were positively correlated to vitamin D-1 and D-2 activities, whereas concentrations of OCPs were negatively associated (Gabrielsen et al., 2015). In East Greenland polar bears, some OHCs were especially important in explaining variation in circulating thyroid hormone levels. BDE99, BDE100, BDE153, CB52CB118, *cis*- and *trans*-nonachlor, and tri- and penta-chlorobenzene, showed both negative and positive relationships with thyroid hormones (Villanger et al., 2011a). Furthermore, thyroid hormone levels in adult male polar bears seemed less influenced by OHC exposure than in females.

Experimental studies on Greenland sledge dogs showed that free and total T3 and T4 were lower in exposed versus control females over 10 months of age, and TT3 was lower at 3 to 12 months of age in exposed pups (Kirkegaard et al., 2011). A positive association between dieldrin and TT3 was also reported. An experimental study on juvenile domesticated Arctic foxes showed no impacts of administered POP exposure for thyroid hormone and thyroid-stimulating hormone (Hallanger et al., 2012). Thus, the thyroid hormone system appears to be affected by OHCs and their metabolites in several Arctic species. However, these effects appear to show sex and age differences.

Since the last AMAP report (Letcher et al., 2010), a number of new studies have focused on the impact of OHC exposure on cortisol. Up to 2009, only a single study investigating 251 Svalbard polar bears had been published (Oskam et al., 2004). The authors concluded that high concentrations of OHCs in polar bears may alter plasma cortisol concentrations. Since then, six publications have become available, focusing mainly on hair cortisol. Bechshøft et al. (2012b) found that hair cortisol concentrations in 23 East Greenland polar bears were correlated with adipose burdens of OHCs, although showing both up- and down-regulation of cortisol levels depending on the specific compound. The down-regulating OHCs included BDE99 and BDE153, CB170/CB190, CB180 and CB201, while those up-regulating cortisol levels were CB66/CB95, α-HCH, heptachlor epoxide, dieldrin, BDE47, and dichlorodiphenyldichloroethane (*p,p′*-DDD). Looking at temporal patterns, Bechshøft et al. (2012a) did not find any obvious OHC impact on interannual hair cortisol levels during a pre- (1892–1927) and post-industrial period (1988–2009) or any trends over the study period. In contrast, cortisol in male Western Hudson Bay polar bear guard hair was found to be positively correlated to Hg when controlling for age and fitness effects, while no relationships were found in females (Bechshøft et al., 2015).

To investigate effects of POPs on steroid hormones in polar bears, blood samples were collected from male and female polar bears in Svalbard in April 2008 (Gustavson et al., 2015; Ciesielski et al., 2017). Associations among circulating levels of specific POP compounds and metabolites (OH-PCBs and OH-PBDEs), steroid hormones, biological and capture variables were investigated. In females, inverse correlations were found between circulating levels of pregnenolone (PRE) and androstenedione (AN), and circulating levels of OH-PCBs (Gustavson et al., 2015). There were no significant relationships between the POPs or their metabolites and the other steroid hormoneshormones, including estrone, 17α-estradiol, 17β-estradiol, dehydroepiandrosterone, testosterone, dihydrotestosterone, or the variables capture date and capture location (latitude and longitude), lipid content, condition and body mass. The increase in PREE and the decrease in AN concentrations suggest that the enzyme CYP17 may be a potential target for OH-PCBs. Although statistical associations do not necessarily represent direct cause–effect relationships, the authors concluded that OH-PCBs may affect the circulating levels of AN and PRE in female polar bears and thus interfere with steroid homeostasis (Gustavson et al., 2015). In males, testosterone was positively related to biometrics, such as body condition index (Ciesielski et al., 2017). Although, a negative relationship was identified between POPs and dihydrotestosterone, none of the other steroid hormones were associated with POP concentrations in plasma of male polar bears (Ciesielski et al., 2017). In an experimental study on Greenland sledge dogs, an over-compensation of levels of reproductive hormones in OHC-exposed female dogs was reported, possibly due to disruption of negative feedback systems (Sonne et al., 2014a). In addition, plasma testosterone concentrations in OHC-exposed juvenile male domesticated Arctic foxes were lower than in control males (Hallanger et al., 2012).

2.1.3. Reproduction and genotoxicity

Previous assessments have outlined the effects of various OHCs on reproductive pathology and potential influences on reproductive performance (Letcher et al., 2010). Since 2010, there have been only

three new studies that examined the effects of POPs on reproduction, and these all in polar bears (Dietz et al., 2015, 2018; Pavlova et al., 2016a, 2016b).

Applying an individual-based modelling approach, Pavlova et al. (2016a,b) explore whether and how PCB-associated reproductive failure could affect the dynamics of a hypothetical polar bear population exposed to PCBs to the same degree as the East Greenland subpopulation. Two alternative types of reproductive failure in relation to maternal ΣPCB concentrations were considered: increased abortion rate and increased cub mortality. The quantitative impact of PCB-induced reproductive failure on population growth rate depended largely on the type of reproductive failure involved. Comparing the model predictions of the age-dependent trend of ΣPCBs in females with actual field measurements from East Greenland indicated that it was unlikely that PCB exposure caused a high incidence of abortions in the specific subpopulation. However, the study could not exclude that PCB exposure might contribute to higher cub mortality. These results highlight the need for further research on the possible influence of PCBs on polar bear reproduction regarding their physiological pathway. This includes determining the exact cause of reproductive failure, i.e. in utero exposure versus lactational exposure of offspring, the timing of offspring death, and establishing the most relevant reference metrics for dose-response relationships. The authors also modelled possible allee effects (correlation between population size and mean individual fitness) in Svalbard bears and concluded that the low representation of 10–14 year-old males among breeding males documented in Svalbard in the mid-1990s could have resulted from PCB contamination.

Dietz et al. (2015) modelled the risk of reproductive impairment and genotoxicity by employing a risk quotient based analysis (RQ = BR/CBR = Body Residue/Critical Body Residue) in OHC-exposed polar bears harvested over the period 1999–2008 in eleven circumpolar subpopulations from Alaska to Svalbard. This RQ evaluation was based on the CBR concept and a physiologically-based pharmacokinetic (PBPK) modelling approach using OHC concentrations measured in polar bear adipose or liver tissue. The total additive RQ from all OHCs was above the toxic effect threshold (i.e., RQ = 1) in all polar bear subpopulations for both endpoints. Risk was lowest in Alaska and highest in East Greenland. For reproductive effects, PCBs were the main contributor, contributing 87–94% and the sum of methylsulfonyl-PCBs (ΣMeSO2-PCBs) – metabolites of PCBs – were the second highest effect contributor (3–5%). For genotoxicity effects, PCBs were likewise the main contributor (71–90%) while perfluorooctane sulfonic acid (PFOS) was the second highest contributor (3–19%).

Lastly, Gilmore (2015) quantified DNA strand breaks in lymphocytes from Svalbard polar bears. Whole blood from 13 males and 34 females was sampled, and lymphocytes were isolated and subject to the comet assay. Baseline strand breaks (tail intensity) ranged from 2% to 18% for males and 7% to 19% for females, with medians of 11% and 13% respectively. Plasma samples were analyzed for PCBs, HCB, β-HCH, *p,p′*-DDE, *p, p′*-DDT, OH-PCBs, oxychlordane, *trans*-nonachlor, PBDEs, and hydroxylated polybrominated diphenyl ethers (OH-BDEs), concentrations of which were within ranges reported earlier. Principal Component Analysis showed a significant negative relationship between DNA strand breaks and a range of PCBs (CB137, CB138, CB156, CB180 and CB183), OH-PCBs (OH-CB-130, OH-CB-146, OH-CB-187), and BDE47. Age, gender and body condition did not appear to affect the level of strand breaks. The authors noted some possible explanations for this observation: (i) increased POP exposure may have led to induced DNA repair and/or antioxidant defense mechanisms, thereby decreasing the number of strand breaks, and (ii) exposure to POPs may have increased the turnover of lymphocytes, thereby changing the relative proportion to cells with lower accumulated damage.

2.1.4. Immunology

The ultimate function of the immune system is to protect the host against infectious diseases as well as aberrant macromolecules such as cancerous cells (Abbas et al., 2012). Resistance to infection requires the concerted effort from the complex network of tissues, cells and molecules that comprise the immune system. Mammalian immunity consists of innate and adaptive responses, which are two separate but interconnected functional arms of the immune system (Fig. 2). Immune responses are also divided into cellular (cell mediated) and humoral immunity. Modulation of both arms of the immune system in marine mammals has been associated with exposure to POPs and metals (Desforges et al., 2016). The previous AMAP report included several studies of immunotoxicity associated with POPs in polar bears from East Greenland and Svalbard as well as in sledge dogs exposed in a controlled feeding experiment (Letcher et al., 2010). These studies found significant effects of POPs on humoral and cellular immunity for these Arctic species suggesting that contaminants may be impairing the ability of animals to respond to infectious pathogens. Since 2010, ten new articles have been published on POPs and Hg and their immune system effects in Arctic marine and terrestrial animals.

In the controlled feeding experiment on West Greenland sledge dogs, exposed pups, but not adults, had reduced and delayed Immunoglobulin G (IgG) antibody production with circulating levels of IgG in all pups correlating to blood concentrations of ΣPCBs, ΣPBDEs and HCB. The specific antibody response to influenza virus, tetanus toxoid and diphtheria toxoid were also measured in the dogs, and reduced antibody production against influenza virus in exposed pups was the only adaptive/humoral parameter reportedly affected (Sonne et al., 2006a). Hepatic mRNA expression of interleukin-1β (IL-1β), an important pro-inflammatory cytokine, in ringed seals from Svalbard and the Baltic Sea was positively correlated with hepatic ΣPOPs (Routti et al., 2010a). Similarly, hepatic IL-1 mRNA expression was positively correlated with blubber ΣPCBs in 41 ringed seals collected by aboriginal hunters in northern Labrador, Canada (Brown et al., 2014). An effect threshold for this immune endpoint in Labrador seals was established at 1.37 μg/g lw.

In vitro T-lymphocyte proliferation after exposure to four PCB congeners (CB138, CB153, CB169, CB180) and two perfluoroalkyl substances, PFOS and PFOA (perfluorooctanoic acid), was assessed in leukocytes collected from lymph nodes of 20 free-ranging ringed seals sampled in East Greenland (Levin et al., 2016). Nonplanar PCB congeners CB138, CB153 and CB180 reduced T-cell proliferation with EC50 (half maximal effective concentration) values of 13.3, 20.7 and 20.8 μg/g, respectively, while the coplanar CB169 had no effect (up to 20 μg/g). Neither PFOS nor PFOA modulated lymphocyte proliferation at concentrations up to 0.3 μg/g wet weight (ww). The authors pointed out that although the EC50 values are typically above observed adipose PCB concentrations in Greenland ringed seals, the threshold effect levels of approximately 1–2 μg/g are commonly exceeded.

In another study, peripheral blood leukocytes were isolated from four captive beluga and used for Hg exposures in in vitro assays of lymphocyte proliferation, intracellular thiol production and metallothionein production (Frouin et al., 2012). Reduced T-lymphocyte proliferation was found at 1 μmol/L Hg and 0.33 μmol/L methylmercury (MeHg) and reduced production of intracellular thiol occurred at 10 μmol/L Hg and 0.33 μmol/L MeHg. Metallothionein was induced by 0.33 μmol/L MeHg, but not by Hg (up to 10 μmol/L). Selenium offered protection in lymphocyte proliferation assays against Hg toxicity only at the highest exposure levels. The authors highlighted that current Hg levels in Arctic beluga fall within the range of exposures that elicited in vitro immune suppression, thus potentially contributing to impaired resistance to infections.

In an extensive study of immunotoxicity in marine mammals using blubber-derived complex contaminant 'cocktails' from polar bears and killer whales, Desforges et al. (2017) reported significant in vitro effects on lymphocyte proliferation, natural killer cell activity, and phagocytosis in lymphocytes from cetaceans, seals and polar bears. This in vitro study found that the polar bear cocktail was more toxic/potent than the killer whale cocktail and related this difference to the contaminant

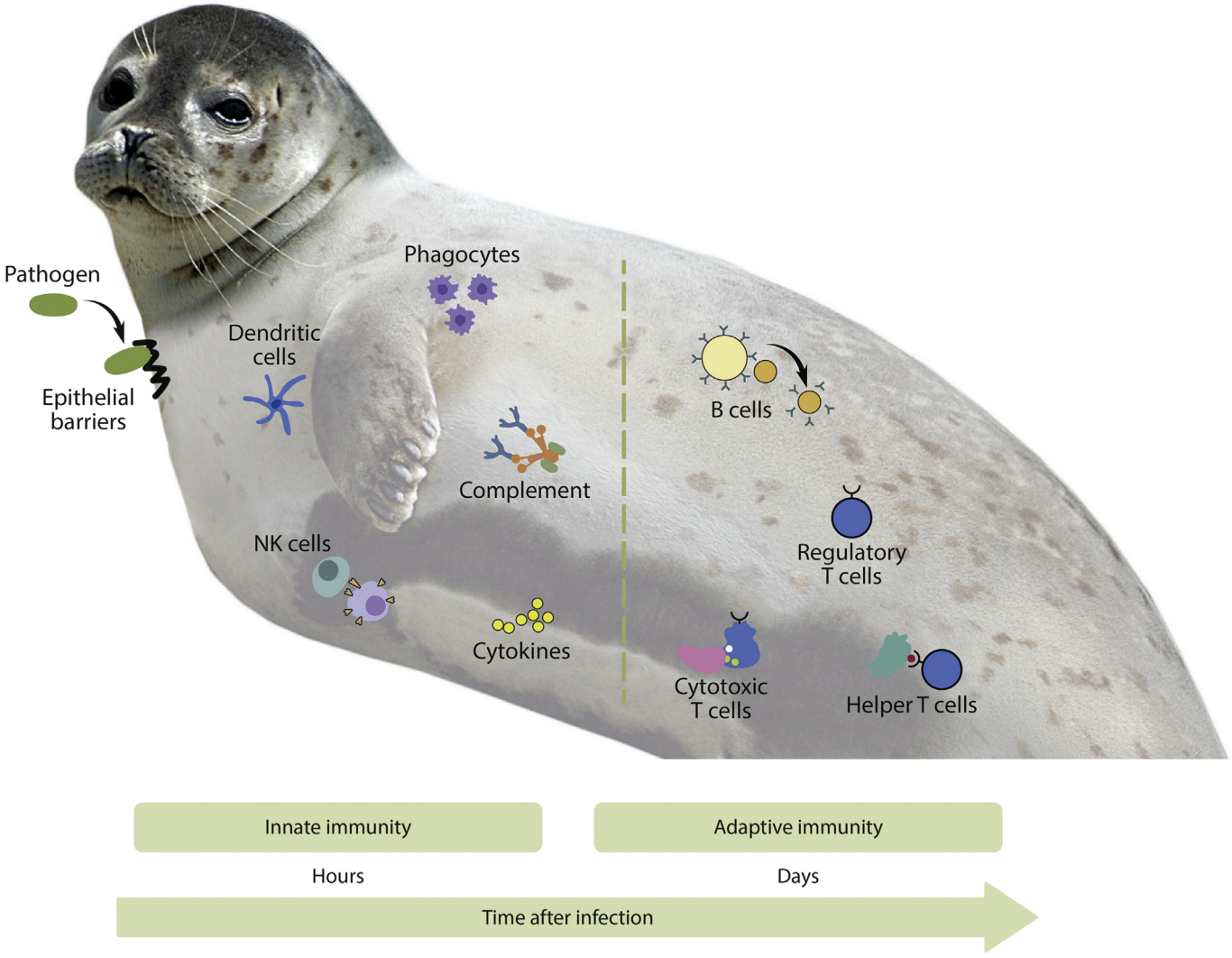


Fig. 2. Cells and molecules of the mammalian innate and adaptive immune system (Modified from Desforges et al., 2016).

composition making up the mixture of compounds, with polar bears having a more pronounced ability to metabolize POPs to potentially more immune active metabolites. For lymphocyte proliferation, the overall marine mammal EC50 values were 0.94 and 6.06 μg/g for the polar bear and killer whale cocktails, respectively. Ultimately, this study reported that in vitro immune effects occurred at lower concentrations using the realistic contaminant mixtures relative to previous studies utilizing single compound exposures.

Finally, in a review and meta-analysis of all immunotoxicity studies of marine mammals to date, including several Arctic species, exposure to environmental pollutants in field studies, captive-feeding studies and in vitro laboratory studies was associated with alterations of the two arms of the immune system, the innate and adaptive, and included cellular and humoral effects (Desforges et al., 2016). Despite differences in study design and animal life history, the review concluded that pollutants, especially PCBs and Hg, systematically suppressed marine mammal immune function. Immune endpoints evaluated in marine mammals fell into several major categories: immune tissue histopathology, hematology/circulating immune cell populations, functional immune assays (lymphocyte proliferation, phagocytosis, respiratory burst, and natural killer cell activity), immunoglobulin production, and cytokine gene expression. Sufficient data were available to calculate effect threshold levels for lymphocyte proliferation and phagocytosis; threshold effect levels for lymphocyte proliferation in polar bears, cetaceans and pinnipeds fell within the range <0.01–10 μg/g lw for PCBs and <0.01–2.4 μg/g ww for metals (Hg, MeHg and CdCd), and 0.6–1.4 (PCBs) and 0.08–1.9 μg/g ww (Hg) in phagocytosis assays. Given the weight of evidence for contaminant-mediated immune suppression, Desforges et al. (2016) concluded that exposure to immunotoxic contaminants may have significant population level consequences as a contributory factor to increasing anthropogenic stress and infectious disease outbreaks.

2.1.5. Skeletal system

Measures and analyses of the skeletal system have gained recognition as valid health endpoints as this organ system can reflect the negative impacts of nutritional and endocrine status. The skeletal system is mainly composed of proteins, calcium, phosphorus and magnesium, and is linked to the maintenance of a dynamic micronutrient homeostatic reservoir (Sarazin et al., 2000; Ganong, 2005). Bone composition and mineral density have been shown to reflect environmental stress, such as exposure to contaminants (Andrews, 1989; Lind et al., 1999, 2000; Jämsä et al., 2001; Lundberg et al., 2006) and starvation (Talbott et al., 2001). Disruptions of the hypothalamic-pituitary endocrine axis may lead to changes in parathyroid hormone, cortisol, steroid and thyroid hormone concentrations that increase bone resorption and to decreased bone formation (Selye, 1973; Colborn et al., 1993; Feldman, 1995; Damstra et al., 2002; Ganong, 2005; Tung and Iqbal, 2007). In

addition, starvation and other energetic-driven stressors may also result in loss of bone density and cause compositional changes (Polischuk et al., 2002; Mustonen et al., 2006). Maintaining a healthy skeletal system is therefore important for Arctic wildlife both at the individual and population level.

The previous AMAP effects report focused mainly on polar bear studies, while controlled studies of captive Arctic fox and sledge dogs did not yield supporting evidence for the polar bear findings (Letcher et al., 2010). In more recent studies, genetic stock differences were found for fluctuating asymmetry and morphology between East Greenland and Svalbard polar bears, while pollutant effects could not be confirmed (Sonne, 2010; Pertoldi et al., 2012). The results suggested that POP exposure probably reduced bone density in skulls and bacula (penile bone) of East Greenland polar bear subadult and adult males, while female skulls did not seem to be affected at all (Sonne, 2010).

In a temporal investigation of polar bear skulls from East Greenland from from1892 to 2010, Sonne et al. (2013b) found that bone mineral density (BMD) had decreased significantly in males over the study period (Fig. 3). Dieldrin had a significant negative association with BMD while DDT, dieldrin and PBDEs were positively correlated with condylobasal length. The reasons for these correlations were not clear, however, given the timing and relationships found, the decrease in skull size and BMD over the past 120 years was likely to have been influenced by a combination of POP exposure and climate change, with selective hunting and genetic changes as possible additional factors. In a similar study design, Daugaard-Petersen et al. (2018) investigated skull size (condylobasal length) and BMD in polar bears from East Greenland (1892–2015) and Svalbard (1964–2004). While BMD in adult males from East Greenland decreased over time, no temporal trend was observed for adult females. Neither was a temporal trend found for BMD or skull size in Svalbard polar bears. The authors also reported no significant difference in BMD between the two populations. When correcting for age and sex, BMD in East Greenland polar bears increased with increasing concentrations of ΣPCB, ΣHCH, HCB and ΣPBDE while skull size increased with ΣHCH concentrations in the period 1999–2014.

A second study on the skeletal system, linked bacula BMD with concentrations of POPs in Canadian and East Greenland polar bears (Sonne et al., 2015a). Size and BMD of penile bones were measured in 279 individuals born between 1990 and 2000 from eight polar bear subpopulations, including seven stocks from the Canadian Eastern Arctic and one in East Greenland. There was a clear latitudinal and longitudinal gradient with Western Hudson bears having the highest BMD and northern East Greenland polar bears having the lowest. The BMD results showed the opposite geographical pattern to POP concentrations, suggesting a possible negative relationship.

2.1.6. Histopathology

Detecting adverse health effects in Arctic animals is not an easy task in such a remote region. Access to plasma and serum samples is often limited due to lack of centrifuges and electricity, which results in limited screening of important health parameters, including diseases. On the other hand, histological screening of various tissues is less cumbersome. Tissues are immediately stored in formaldehyde with alcohol to prevent freezing artifacts. Tissue alterations and lesions may be observed on later examination, and as needed, interpreted in relation to a broad suite of different biological and chemical parameters (Sonne, 2010). Such analyses may provide an indication of the specific organ status, the value of which is important for Arctic wildlife at both the individual and population level.

The liver is a target organ as many chemical contaminants concentrate there. The liver is also susceptible to toxic damage because it is the main organ to metabolize accumulated chemical contaminants. In this metabolic chain reaction, metabolites are produced that may be

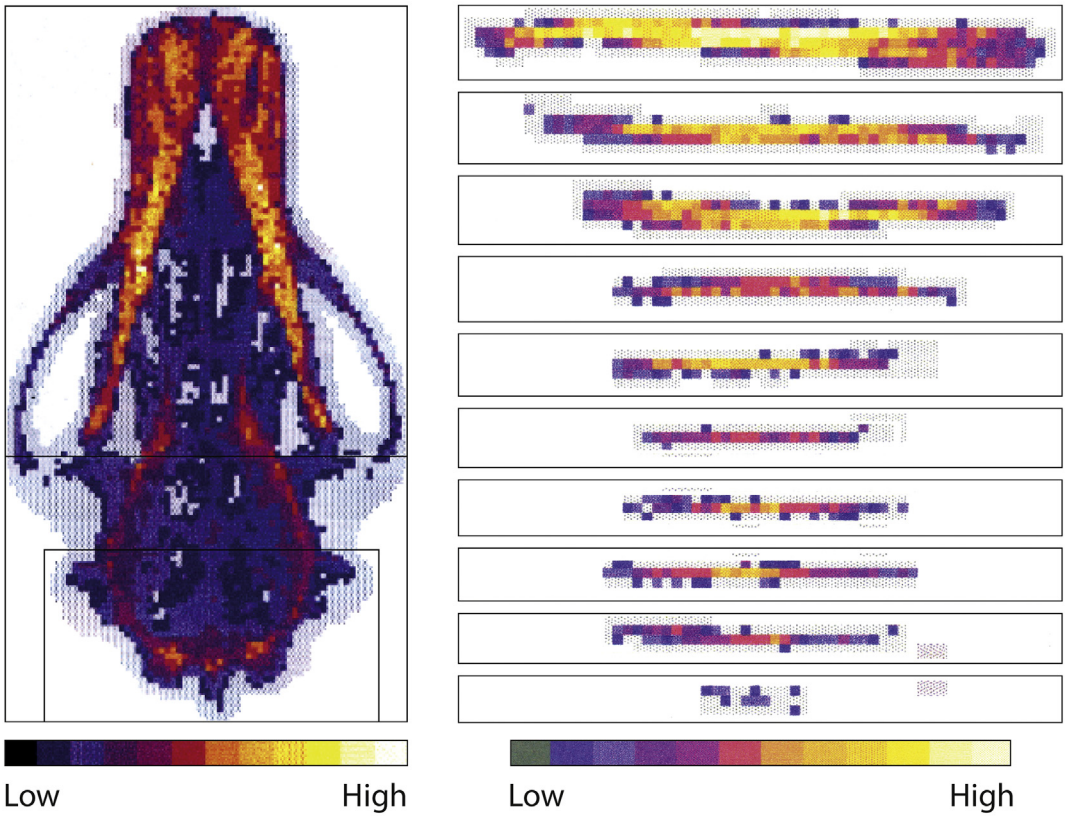


Fig. 3. Dual energy x-ray absorptiometry (DEXA) scanning images of (left) a 12-year-old female East Greenland polar bear skull sampled in 1972 and (right) polar bear penilele bone/baculum from ten Canadian polar bears aged 2–28 years sampled in the period 1997–2003 (modified from Sonne et al., 2004, 2006b). Bar colour denote low density (dark blue) and high density (light yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

even more cytotoxicity than the parent compound (Letcher et al., 2010). This means that despite the large metabolic and detoxifying capacity of the liver, lesions are often seen in this organ due to oxidative stress and metabolic disorders (Al-Saleh et al., 2003; Klaassen et al., 2007). The actual effects of chemical contaminant exposure are hard to distinguish since they may elicit or mimic reactions to other stressors from external/environmental factors. Effects are divided into direct cellular toxicity and indirect toxicity mediated by a disruption in various endocrine and immunological feedback systems (Letcher et al., 2010; Sonne, 2010; Dietz et al., 2013c). The kidney is also an important organ for multiple vital functions including clearance of metabolic waste products, and homeostatis of water and electrolytes, thereby supporting blood pressure maintenance, vitamin D production and calcium homeostasis (Ganong, 2005). Chronic kidney damage may therefore disrupt bone density and clearing of metabolic waste products from blood. Such impacts may be detected via specific analytical modalities (Maxie, 1993; Confer and Panciera, 1995; Klaassen et al., 2007). Since the previous AMAP assessments, seven articles have been published on histopathology in relation to contaminant exposure in Arctic marine and terrestrial mammals. Overall, the results suggest that liver and renal alterations in polar bears, in addition to the chemical contaminant exposure, are likely to be due to a combination of age and recurrent infections.

Sonne et al. (2012a) were the first to present information on histopathological effects over a longer time period. Liver and kidney samples from 122 East Greenland polar bears were examined over the 12-year period 1999–2010 where the prevalence of various liver and kidney lesions were reported in association to adipose PCB concentrations (5674–17,591 ng/g lw).Of these, fat accumulation in the liver, kidney cell infiltrations, glomerular sclerosis and tubular hyperplasia decreased, while detectable liver Ito cells, kidney glomerular capillary wall thickening, and interstitial fibrosis increased over time. Several of these observed tissue alterations were either positively or negatively correlated with adipose concentrations of Hg and POPs. Thyroid glands were examined in a smaller number of individuals ($n = 20$) around the same period (Sonne et al., 2011) (Fig. 4) and the analyses found that 12 polar bears had normal thyroid tissue, while the remaining eight had C-cell proliferations, nodular hyperplasia or interstitial fibrosis. There were however, no significant differences in POP concentrations between individuals with and without lesions. The observed lesions in polar bears were similar to those found in POP-exposed laboratory animals and other highly contaminated wildlife, and were likely to be the combined result of POP exposure, normal metabolism- and thermoregulation, autoimmunity or infections. The authors could not exclude the possibility that lesions were coincidental idiopathic alterations due to hypothalamic-pituitary-thyroid axis interactions.

The histopathology of livers and kidneys has also been investigated in Faroese pilot whales ($n = 14$), Greenland narwhal ($n = 19$) and ringed seals ($n = 40$) (Sonne et al., 2010a, 2013a, 2018). Chemical analyses showed PCB (13947–34,543 ng/g lw) and Hg (54–351 μg/g ww) concentrations in pilot whale blubber and liver to be high compared to other marine mammals, which coincided with a high prevalence (>35%) of both renal and liver lesions similar to those previously found in contaminated Arctic marine mammals (Sonne et al., 2010a). Studies of narwhal revealed lower liver Hg concentrations (0.4–32 μg/g ww), but nevertheless similar histological changes in this tissue as found in other histological contaminant studies of Arctic mammals (Sonne et al., 2013a, 2018). A single study on ringed seals reported hepatic Hg levels in Thule (0.28–23.3 μg/g ww) and Godhavn (0.45–8.0 μg/g ww) which correlated with the occurrence of hepatic hemosiderosis. The authors suggested that the histopathological changes were likely to be the combined result of age and contaminant exposure, with contaminant exposure acting as an aggravating co-factor in the development of tissue lesions. However, larger studies are required to determine the influence of natural versus anthropogenic factors on

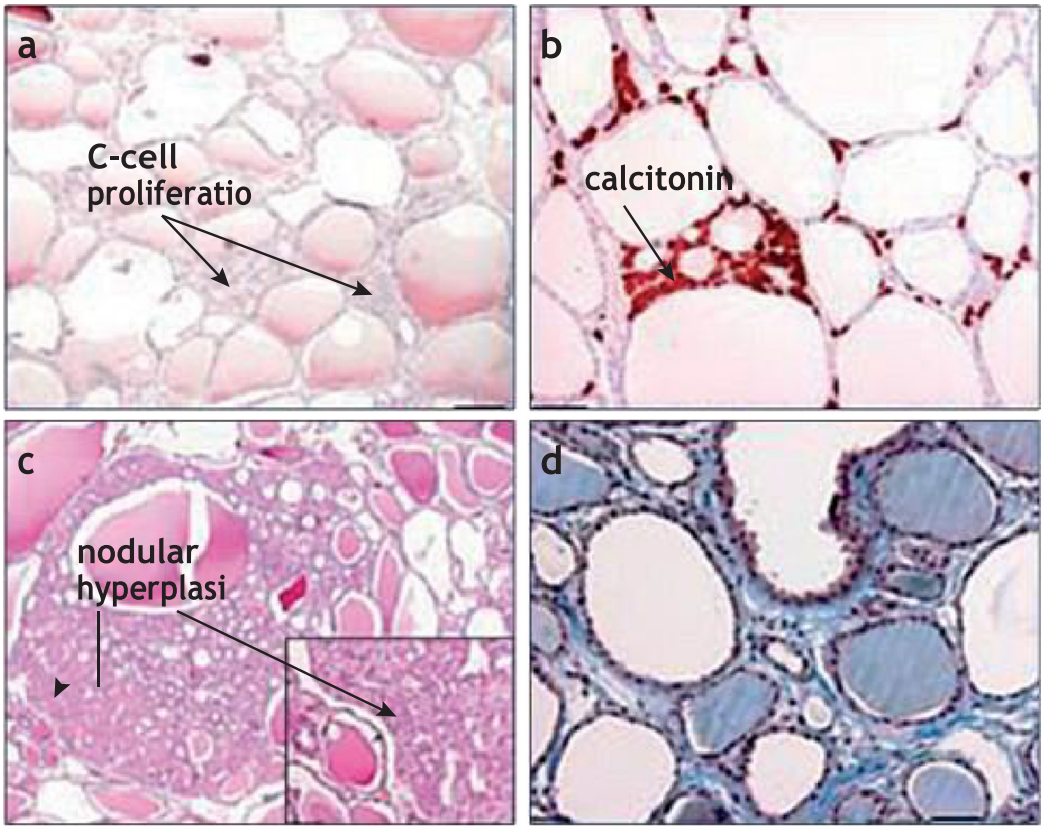


Fig. 4. Thyroid lesions in East Greenland polar bears sampled during 1999–2009. (a) C-cell proliferations. (b) calcitonin colouring. (c) nodular hyperplasia. (d) interstitial fibrosis. (Modified from Sonne et al., 2011).

liver and kidney histopathology. Likewise, efforts could be made to resolve the issue of extrapolating histopathological changes to particular health effects, as well as effects at the population level.

In a controlled study on a female sled dog cohort fed marine food items, a physiologically-based pharmacokinetic (PBPK) model was developed to estimate the risk of POP exposure on various health endpoints (Sonne et al., 2015b), allowing the estimation of RQs for POP exposure and potential effects. The PBPK model confirmed that POPs induced liver histopathological effects. In 75% of the dogs, dieldrin was detected in concentrations sufficient to induce pathological changes in liver tissue followed by ΣCHLs > ΣPCBs > ΣDDTs > ΣPBDEs > HCB > ΣHCHs. The authors concluded that RQs based on adipose tissue concentrations were the best reflector of health effects, and suggested that this metric could be used in future risk assessments of POP exposure in Arctic top predators. Altogether, these studies on terrestrial and marine mammals point towards POPs and Hg as co-factors in the development of liver, kidney and thyroid lesions.

In the only study of wild terrestrial mammals, Larter et al. (2016) reported Hg to be higher in mountain caribou (*Rangifer tarandus caribou*) than moose (*Alces alces*), although levels were much lower than for cadmium (<1.0 μg/g ww). Minor histological changes in the proximal tubules and glomerulus of the kidney were found in each species, although such changes were rare and did not indicate damage consistent with metal accumulation. The authors concluded that while elevated Cd levels did not appear to cause pathological damage in these terrestrial mammals, there remained significant implications for northern populations who consume terrestrial country foods.

2.1.7. Neurotoxicology

The neurotoxicological potential of MeHg is firmly established with well-characterized human poisoning events in Japan, Iraq, and Brazil (Mergler et al., 2007). Similarly, for OHCs there is an established and growing literature base showing that, for example, exposure to PCBs and PBDEs is associated with adverse neurological outcomes (Mariussen and Fonnum, 2006). High-trophic level, fish-eating wildlife species can biomagnify contaminants such as PCBs and PBDEs, which have been shown to elicit exposure-associated neurological effects (Basu and Head, 2010; Basu, 2012, 2015). Although many studies show Arctic marine mammals can bioaccumulate substantial levels of MeHg and OHCs, little is known about their uptake into brain tissue. This makes it difficult to establish potential health effects.

Recent studies have emerged that characterize Hg levels in brain tissues of Arctic marine mammals. In one of the first studies on potential neurological effects of Hg, total Hg and MeHg levels were measured in the brain stem region of 82 polar bears collected by subsistence hunters in Greenland (Basu et al., 2009). Concentrations of total Hg were found to be <1 μg/g dw. In this same brain region, MeHg comprised 82.8% of the total Hg load. Similar total Hg levels were reported for the brain stem of Canadian polar bears (Krey et al., 2012), as well as the finding that nearly all Hg in these tissues occurred in the methylated form. In follow-up studies, Hg levels were characterized in ten brain regions (pituitary, occipital cortex, frontal cortex, cerebellum, brainstem, thalamus, hypothalamus, temporal cortex, hippocampus, basal ganglia) from polar bear, narwhal, ringed seal, pilot whale, and harbor porpoise (*Phocoena phocoena*) (Basu, pers. comm.). In all cases, mean total Hg levels were highest in the pituitary and lowest in the brain stem. A study by Krey et al. (2015) comparing total Hg levels in the cerebellum and frontal cortex found no differences for ringed seal, polar bear, and beluga. In the aforementioned study, mean MeHg levels as a percentage of total Hg ranged from 51% to 96%. Notably, MeHg in the pituitary was <50% of total Hg. In the cerebellum and frontal cortex of ringed seal and polar bear, MeHg represented over 90% of total Hg but in beluga was only about 12% (Krey et al., 2012). These studies point to interesting differences across species. Brain Hg levels are consistently lowest in ringed seal and polar bear, and across all brain regions studied in these species. Brain Hg levels in pilot whale, harbor porpoise, and narwhal are much higher and range at upwards of 80 μg/g dw, levels associated with clinical neurotoxicity in mammals (Basu, 2012, 2015).

Much less is known about the uptake of OHCs into the brain tissues of Arctic marine mammals. Gebbink et al. (2008) measured a large suite of chlorinated and brominated contaminants and their by-products in brain tissue of East Greenland polar bears. They found that compared to liver, blood and adipose, the lowest OHC concentrations consistently occurred in the brain, often below method detection limits. The authors estimated that the OHC burden in the brain accounted for approximately 0.002% of the total amounts in the four body compartments studied. This suggests that the blood-brain barrier may effectively limit neural exposure to certain OHCs in polar bears.

In the first study of its kind at the time, Greaves et al. (2012) investigated the comparative accumulation of perfluoroalkyl acids (PFAAs) in eight brain regions of polar bears collected in 2006 from East Greenland. On a wet-weight basis, blood–brain barrier transport of PFAAs occurred for all brain regions, although inner regions of the brain closer to incoming blood flow (pons/medulla, thalamus, and hypothalamus) contained consistently higher PFAA concentrations compared to outer brain regions (cerebellum, striatum, and frontal, occipital, and temporal cortices). For pons/medulla, thalamus, and hypothalamus, the most concentrated PFAAs were perfluorooctane sulfonate (PFOS) and perfluorotridecanoic acid. Longer-chain perfluorinated carboxylic acids (PFCAs; C10–C15) were significantly positively correlated with lipid content for all brain regions. The study demonstrated that both PFCAs and perfluoroalkyl sulfonates (PFSAs) cross the blood–brain barrier in polar bears and that wet-weight concentrations are brain region-specific. In a follow-up study on PFASs in several brain regions of polar bears from East Greenland collected in 2011–2012 (Pedersen et al., 2015, 2016), the most abundant PFAS was again PFOS and accounted for approximately 90% of ΣPFSAs. The highest concentrations of PFASs were measured in brainstem, cerebellum and hippocampus.

There have been a few new studies on Arctic marine mammals that have attempted to relate contaminant exposure with neurological effects using neurochemical biomarkers. In vitro studies on brain tissue extracted from polar bears (Krey et al., 2014) and ringed seals (Basu et al., 2006a) have shown Hg to inhibit binding of neurochemical receptors and activity of neurochemical enzymes of physiological importance. Extrapolating these in vitro findings to the whole organism has proved more challenging. For example, neither Krey et al. (2014) nor Basu et al. (2009)observed any Hg-associated changes in brain cholinergic receptors or enzymes despite in vitro evidence showing potential effects as well as previous in vivo results on mink (*Mustela vison*) (Basu et al., 2006b), bald eagles (*Haliaeetus leucocephalus*), and common loons (*Gavia immer*) (Scheuhammer et al., 2007) pointing to exposure-related changes. In another study, a negative association was found between brain Hg levels and *N*-methyl-D-aspartate (NMDA) receptors in the brain stem of polar bears (Basu et al., 2009), as previously seen in in vivo- and naturally-exposed mink (Basu et al., 2007) and in wild eagles and loons (Scheuhammer et al., 2007). In a study of beluga using both biochemical and molecular approaches, Ostertag et al. (2014) found a number of Hg-associated changes in components of the GABAergic and glutamatergic systems. Fewer studies have examined OHC-associated effects on Arctic marine mammal neurochemistry. In a study of brain stem tissues of polar bears, several chlorinated and brominated organic chemicals were not observed to associate with neurochemical biomarkers (Basu et al., 2009). In a study of multiple polar bear brain regions sampled in East Greenland in 2011 and 2012, correlations were found between PFSA/PFCA concentrations in polar bears and the neurochemical biomarkers from cholinergic, glutaminergic, GABAergic and dopaminergic systems, for example monoamine oxidase and GABA-A receptors (Pedersen et al., 2015). These correlations may be an indication of early adverse changes in neuro-behavior and animal health. The authors recommended that further studies be performed to investigate the neurotoxic effects of PFASs (especially PFCAs) on Arctic mammals, including the polar bear.

In a recent study, Pedersen et al. (2016) investigated whether PFAS could induce alterations in brain steroid concentrations in the same East Greenland polar bears. This study showed significant positive correlations across all brain regions between 17α-hydroxypregnenolone (OH-PRE) and all investigated PFASs; PFOS, ΣPFSAs, perfluoro-*n*-undecanoic acid (PFUnDA), perfluoro-*n*-dodecanoic acid (PFDoDA), perfluoro- *n*-tridecanoic acid (PFTrDA) and ΣPFCAs. Positive correlations were found between ΣPFCAs and several steroid hormones in the occipital lobe. Positive correlations between PFCAs and steroids were especially evident for pregnonelone, progesterone, OH-PRE, DHEA, androstenedione and testosterone. The results generally indicated that an increase in PFAS concentrations seems to coincide with an increase in steroid hormones in East Greenland polar bears. However, it is not possible to determine whether alterations in brain steroid concentrations arise from interference with de novo steroid synthesis or via disruption of peripheral steroidogenic tissues mainly in gonads and feedback mechanisms.

2.1.8. Bioenergetics

There have only been six studies reporting on contaminants and effects on parameters related to bioenergetics in Arctic mammals since 2010. Castelli et al. (2014) reported transcript levels of genes related to lipid metabolism in highly contaminated Baltic ringed seals and less contaminated seals from Svalbard. Transcript levels of genes that stimulate lipid accumulation, peroxisome proliferator-activated receptor gamma (PPARG) and its target genes, were higher in Baltic seals compared to seals from Svalbard, and increased with contaminant exposure. Transcript levels of genes related to lipid metabolism (PPARG, adiponectin, leptin) were not related to PCB exposure in killer whales from British Columbia, Canada, or beluga from the Beaufort Sea (Buckman et al., 2011; Noel et al., 2014). Tartu et al. (2017a) performed an extensive study on female polar bears from Svalbard including abundance profiles for nine lipid-related genes, fatty acid synthesis and elongation indices in adipose tissue, and concentrations of lipid-related variables in plasma (cholesterol, high-density lipoprotein, triglycerides), in addition to plasma metabolomics and lipidomics. The results based on multiple end-points indicated that several OHCs affect lipid biosynthesis and catabolism in female polar bears. More pronounced effects were noted when combined with reduced sea-ice extent and thickness, suggesting that climate-driven sea-ice decline and OHCs have synergistic negative effects on polar bears.

Lille-Langøy et al. (2015) constructed an in vitro assay to study activation of polar bear pregnane X receptor (PXR), which is involved in metabolism of glucose and lipids in addition to biotransformation, whereas Routti et al. (2016a, 2016b) constructed an assay expressing polar bear PPARG. Several contaminants found at high concentration in polar bears, for example CB153, activated PXR, whereas the most abundant POPs found in polar bear adipose tissue (CB153, oxychlordane), as well as a POP mixture that reflects concentrations in polar bears, decreased PPARG activity. Furthermore, contaminant mixtures extracted from polar bear tissues enhanced lipid accumulation stem cells derived from in polar bear adipose tissue as well as in mouse cells (Routti et al., 2016a, 2016b). However, a synthetic mixture of POPs did not affect lipid accumulation in the polar bear or mouse cells. Further characterization using non-target screening showed that emerging compounds that have been shown to induce lipid accumulation, such as phthalates, tonalide and nonylphenol, were present in the extracts (Routti et al., 2016a, 2016b).

Seasonal mobilization of lipids from fat depots may have a strong influence on concentrations and tissue distribution of POPs in Arctic mammals. An experimental study on farmed Arctic foxes reported that PCB and CHL concentrations increased 19 and 25 fold in blood after emaciation, whereas increase in liver and other tissues was seven fold or less (Helgason et al., 2013). Studies on free-ranging Arctic foxes from Svalbard indicate that concentrations of lipophilic POPs and OH-PCBs increase with decreasing body condition (Andersen et al., 2015; Routti et al., 2016a, 2016b). Concentrations of PCBs, CHLs and OH-PCBs were approximately 3–4 times higher in thinnest compared to fattest foxes. Comparison of PFAS concentrations in different tissues of lean and fat free-ranging Arctic foxes from Svalbard indicated that PFCAs and PFSAs were several times higher in adipose tissue of lean compared to fat foxes (Aas et al., 2014). Additionally, few individual PFASs (PFDA, PFHpS and PFNA) were twice as high in liver and blood of the lean compared to the fat foxes. The results suggest that toxic potential of POP and PFAS exposure may increase during seasonal fasting.

For polar bears, Jenssen et al. (2015) emphasized that one of the main effects of climate warming is limited access to seals – their main prey – due to loss of their sea-ice habitat, which can be viewed as a perturbation of the bears' bioenergetic homeostasis. This will result in prolonged fasting periods that are likely to result in emaciation and condition-related negative effects on survival and reproductive success. Prolonged fasting, and especially emaciation, will result in increased POP concentrations in polar bear tissues, with an increased likelihood of POP levels exceeding threshold levels for effects on health, and thus potentially affecting reproductive success and survival. Tartu et al. (2017b) demonstrated that sea-ice associated decline in body condition was related to increased concentrations of lipophilic POP in plasma and adipose tissue from female polar bears from Svalbard. The authors observed these associations both at seasonal and spatial scale. Polar bears were in poorer condition and had higher POP levels following a winter with little sea ice than a winter with "normal" sea ice conditions. Also, in areas where sea ice was scarce, bears were thinner and had higher concentrations of POPs. Concentrations of PFAS, on the other hand, were not affected by body condition in polar bears, but were higher in fasting than in non-fasting bears (Tartu et al., 2017c).

2.1.9. Clinical chemistry

Few new studies appear to have been reported on the effects of OHC and Hg exposure on clinical chemistry in Arctic marine and freshwater mammals since previous effects assessment reviews (Letcher et al., 2010; Dietz et al., 2013a). However, along with a range of POPs, a suite of 12 specific blood clinical-chemical parameters (BCCPs) were analyzed in 20 female and 18 male Svalbard polar bears (*Ursus maritimus*) captured in spring 2007 (Ciesielski et al., 2018). The results showed that in the females, hematocrit and high-density lipoproteins were significantly correlated with the plasma concentrations of several POPs. However, age, body condition, plasma, lipid content, and geographical location (longitude and latitude) were also important parameters explaining BCCPs in females. In males, hematocrit, aspartate aminotransferase (important for amino acid metabolism), the liver enzyme γ-glutamyltransferase, and cholesterol were significantly correlated with plasma levels of several POPs. Similar to females, age, body mass, body condition, and longitude were important factors explaining the variation in the BCCP values in males. It was concluded that biological confounding factors need to be considered when studying the possible effects of POPs on BCCPs in polar bears. After correcting for these confounding factors, it was determined that hematocrit in particular may be used as a simple cost-efficient biomarker of POP exposure in polar bears. Furthermore, decreasing high-density lipoprotein concentrations and increasing cholesterol concentration with increasing POP concentrations may indicate responses related to increased risk of cardiovascular disease (Ciesielski et al., 2018).

2.2. Marine and terrestrial birds

2.2.1. Vitamins and oxidative stress

At the time of the previous AMAP effects report (Letcher et al., 2010; Dietz et al., 2013a, 2013b, 2013c), there had been studies for a few species and populations of marine birds in the Arctic linking tissue contaminant burdens to circulating and tissue vitamin levels as well as oxidative stress. These included ivory gull (*Pagophila eburnea*), black-legged kittiwake (*Rissa tridactyla*), and common eider (*Somateria*

mollissima) (Miljeteig et al., 2009; Murvoll et al., 2006; Murvoll et al., 2007). Since 2009, there have been a few new published reports on contaminants in relation to vitamins in ivory gulls and northern fulmars (*Fulmarus glacialis*) from the Arctic. Using a meta-analysis approach, the variations in retinoids were investigated in northern fulmars that breed in three populations differentially exposed to OCs: Nunavut (Canadian Arctic), Svalbard (Norwegian Arctic) and the Faroe Islands (Verreault et al., 2013). OC levels were found to be substantially higher in the liver of birds breeding in the Faroe Islands than in birds breeding in Svalbard and Nunavut. Furthermore, concentrations of PCBs, PCDDs, PCDFs, HCB, *p,p′*-DDE and oxychlordane in the liver were positively correlated with hepatic retinyl palmitate levels. These retinyl palmitate levels were significantly associated with decreasing plasma retinol levels as well as somewhat unchanged liver retinol levels. It was concluded that these three geographically-distant sites of breeding fulmars show that organochlorine exposure (mainly PCBs and dioxins/furans) may be associated with modulation of the thyroid and retinoid homeostasis. Effects of confounding environmental factors (such as temperature and nutritional status) on physiological variables could not be ruled out, and thus cause-effect linkages between retinoid system perturbation and OC exposure could not be determined.

In a follow up study by Miljeteig et al. (2009) on ivory gull eggs from Svalbard and the Russian Arctic, associations were reported between high levels of contaminants (OCPs, PCBs, BFRs, PFASs, Hg) and three response variables: eggshell thickness, retinol and α-tocopherol (Miljeteig et al., 2012). Negative associations were found between levels of OCPs, PCBs, and BFRs and eggshell thickness and α-tocopherol, but not with retinol. There were no associations between PFASs and Hg and the three response variables. Furthermore, eggshell thickness was 7–17% thinner compared to archived ivory gull eggs (from before 1930). In general, thinning of >16–20% has been associated with a decline in bird populations, suggesting that contaminant-induced eggshell thinning may constitute a serious threat to ivory gull populations globally.

Braune et al. (2011) examined relationships between hepatic concentrations of OHCs and vitamin A concentrations in liver as well as retinol levels in blood plasma of northern fulmars at two breeding colonies in the Canadian High Arctic. Biomarker levels or responses did not differ significantly between males and females at either colony, nor were there any significant differences between colonies. No significant relationships were found between hepatic retinoid concentrations and any of the dioxin-like compounds or their toxic equivalents (TEQs) although significant positive correlations were found with plasma retinol. Helgason et al. (2010) investigated whether liver retinoid concentrations were explained by liver and blood levels of OHCs in free-ranging breeding northern fulmars from Bjørnøya in the Norwegian Arctic. Results showed no strong relationships between OHC concentrations and liver vitamin A levels in the breeding birds. It was suggested that the OHC levels were too low to affect liver levels of retinal and retinyl palmitate.

OHCs may have adverse effects on the health of birds, especially marine avian top predators that accumulate high OHC loads. Contaminants may influence the antioxidant enzyme activity (oxidative stress). Moreover, physical conditions and oxidative stress during development may reduce telomere lengths, one of the main mechanisms explaining cell senescence. Since 2009 there have been quite a few new published reports on contaminants in relation to oxidative stress in birds from the Arctic showing that food composition and exposure to environmental contaminants may affect antioxidant responses (Hegseth et al., 2011a, 2011b, 2011c, 2014). Sletten et al. (2016) examined the potential effects of environmental contaminants on physiological biomarkers of health in white-tailed eagles (*Haliaeetus albicilla*) in the Norwegian subarctic. OHCs with different physicochemical properties were related to superoxide dismutase enzyme (SOD) activity in blood plasma, and telomere length (measured in red blood cells) in individual 7- to 8-week old nestlings. Different organochlorines and PFASs were measured in blood plasma of nestlings, demonstrating higher concentrations of PFASs and notably PFOS as compared to legacy organochlorines. There were significant, negative relationships between OHC loadings and SOD activity suggesting that some legacy OHCs challenge the antioxidant capacity in nestlings of white-tailed eagles.

Bourgeon et al. (2012) reported on the contribution of legacy OHCs and PBDEs to individual variations in oxidative stress occurring in three breeding colonies of a top predator seabird, great skua (*Stercorarius skua*), distributed from temperate regions to the High Arctic: Shetland Islands, Iceland and Bjørnøya. Plasma concentrations of OHCs in great skua from Bjørnøya were among the highest in North Atlantic seabirds. A latitudinal gradient in OHC levels was observed with all compounds being significantly higher in Bjørnøya than in Iceland and the Shetland Islands. Skuas breeding at the least contaminated site (Shetland Islands) experienced 50% higher oxidative stress compared to the two other colonies. However, the authors' results failed to identify consistent within-colony relationships between biomarkers of health. It was suggested that other ecological factors such as food availability were constraining the physiological indicators more than anthropogenic contaminants.

Wayland et al. (2010) investigated glaucous gulls (*Larus hyperboreus*) from the Canadian Arctic in terms of relationships between OCPs, PCBs, Hg and Se, and measures of oxidative stress (glutathione [GSH] metabolism and lipid peroxidation). Contaminant levels were low and associations between contaminant exposure and oxidative stress were weak. Nevertheless, levels of thiols declined as Hg and OCP/OCPPCB levels rose (glutathione peroxidase activity rose with increasing hepatic Se concentrations) and at one of the two study sites levels of lipid peroxidation were elevated with increasing levels of hepatic Hg. It was suggested that there was possible deleterious effect of exposure to contaminants on gull physiology even at low exposures.

2.2.2. Endocrinology

Exposure to endocrine-disrupting chemicals may alter the ability of Arctic animals to adapt to ongoing environmental change (Jenssen, 2006). In polar regions including the Arctic, where the productive summer season is short, proper endocrine regulation of the timing of breeding, molting, and migration is especially important. Since the last AMAP effects report there have been a few new studies on contaminants and endocrine effects in Arctic birds, including investigations on glucocorticoids, thyroid hormones, and steroid hormones.

Glucocorticoids are involved in a range of physiological processes including reproduction, behavior, adaptation to stress, and immunology (Wingfield and Sapolsky, 2003). More specifically, the release of the hypothalamic–pituitary–adrenal axis-mediated corticosterone (CORT) during stressful events triggers physiological and behavioral adjustments that redirect energy investment away from reproduction towards self-preservation and survival (Wingfield and Sapolsky, 2003). Release of the anterior pituitary hormone prolactin stimulates parental behavior, such as brood provisioning and egg incubation (Buntin, 1996), and has been shown to decrease during acute stress responses (Chastel et al., 2005). In male glaucous gulls, baseline prolactin levels and the rate of decrease in prolactin after a restraint protocol seem to vary negatively with plasma OHC concentrations (OCPs, PCBs, BFRs, and associated metabolic products), and were found to be significant for PBDEs only (Verreault et al., 2008).

Nordstad et al. (2012) found ΣPCB concentrations to be positively associated with baseline plasma CORT concentrations during the prelaying period of black-legged kittiwakes at Svalbard. Yet, the plasma CORT- PCB relationship in black-legged kittiwakes seems sensitive to a number of factors, including environmental conditions, sex and breeding status. Several studies have investigated CORT-PCB relationships in plasma of kittiwakes during different years, on both sexes and at different breeding periods (Nordstad et al., 2012; Tartu et al., 2014a, 2015a, 2015b). The overall pattern is an increase in CORT with increasing ΣPCB concentrations, although the authors did not find a relationship

between CORT and ΣOCPs. The underlying mechanism associating plasma CORT to plasma ΣPCB levels could result from the detoxification process loop. High levels of PCBs can induce the expression of cytochrome P450 enzymes, which can catalyze the transformation of steroids leading to the formation of, among others, glucocorticoids. A precursor of costicosterone for example would be 11-deoxycosticosterone. Thus, glucocorticoid levels can be increased via POP exposure. For example, the activation of receptors for adrenocorticotropic hormones were associated with PCB concentrations in exposed Arctic seabirds (Tartu et al., 2015a).

The association between CORT and ΣPCB is likely to be species-specific) Tartu et al. (2015a) did not observe any effect of PCBs on baseline or stress-induced CORT levels in common eiders. However, they did see a lowered stress-induced release of plasma CORT in glaucous gulls with higher blood PCB levels, meaning that the use of CORT as a bioindicator may be constrained by ecological factors. This was in fact emphasized by Bourgeon et al. (2012) studying great skua in the High Arctic. They showed feather CORT levels to be highest in the least POP-contaminated colony, and inter-individual associations between feather CORT and plasma POP levels to be non-existant. Finally, Tartu et al. (2014a) studied the effects of PFASs in adult chick-rearing black-legged kittiwakes. In contrast to what was found for restricted OHCs (Nordstad et al., 2012; Tartu et al., 2014a) baseline plasma CORT concentrations were negatively associated with some PFASs during the chick-rearing period. In contrast to PCBs (Nordstad et al., 2012), PFASs may disrupt the hypothalamic– pituitary–adrenal axis resulting in lower ability to secrete sufficient baseline concentrations of CORT. Nonetheless, the absence of a significant relationship between PFAS levels and stress-induced plasma CORT concentrations may indicate this association to reflect hormone displacement due to high protein affinity of PFASs.

Thyroid hormones regulate metabolic processes, thermogenesis, and the growth and differentiation of tissues, including the regulation of neuronal proliferation, cell migration, and differentiation of the developing animal (Zoeller et al., 2002). In birds, thyroid hormones are also central in regulating molting and replacement of feathers (Kuenzel, 2003; Leeson and Walsh, 2004). Northern fulmars in the Canadian High Arctic did not show any significant association between plasma total thyroxine (TT4) and hepatic OC or PFAS concentrations (Braune et al., 2011). For total triiodothyronine (TT3), there was a significant negative association with hepatic dichlorodiphenyldichloroethane (DDD) only, largely supporting observations on northern fulmar from Bjørnøya in the Norwegian Arctic, for which no associations between plasma total and free T3 and T4 or hepatic OC levels were found (Helgason et al., 2010). The lack of significant associations may be concentration dependent, as breeding adult glaucous gulls at Bjørnøya showed free and total plasma T4 levels (Verreault et al., 2004), as well as the T4:T3 ratio to be negatively impacted by OCs (Verreault et al., 2004, 2007). Many chemicals, including PCBs, alter the ratio of T4:T3 by direct action on the thyroid gland by interference with transport proteins, such as transthyretin or albumin, or by inhibition of the peripheral conversion of T4 to T3 by deiodinases and increase in glucuronidation and excretion (Rattner et al., 1984). Therefore, the ratio of T4:T3 is indeed a sensitive indicator of contaminant exposure (Peakall, 1992). However, the positively associated ratio of TT4:TT3 to hepatic concentrations of DDD in Canadian northern fulmar (Braune et al., 2011) contrasts with observed negative associations in Norwegian glaucous gull (Verreault et al., 2004, 2006). Another interesting biomarker is the TT4:FT4 and TT3:FT3 ratios as they were reported to be negatively impacted by organochlorines and PFASs (Nøst et al., 2012). Interestingly, the latter study found black-legged kittiwake and northern fulmar chicks at Svalbard to show positive associations between free and total plasma T4 and T3 and plasma PFASs and OCs, respectively. Although a positive association to hepatic PFCAs was also found in Canadian northern fulmar (Braune et al., 2011), similar to the above-mentioned CORT (Tartu et al., 2014a, 2014b), this dynamic is often believed to be the result of a common affinity for protein binding, which is particularly high for T3 in birds (McNabb, 2007), rather than PFASs being disruptive to thyroid function which would be reflected by a negative relationship. Interestingly, two recent studies show that OCs and PFAS may affect the energy metabolism through the function of thyroid hormones in each direction (Blevin et al., 2017; Melnes et al., 2017).

The glaucous gull at Bjørnøya is a well-studied population, and positive associations have been found between POPs, more- specifically methoxy-PBDEs, PCBs, chlordanes, HCHs, mirex, OCPs, PBDEs and hexabromocyclododecane (HBCD) isomers, and levels of testosterone and 17β-estradiol in yolk, as well as between PBDEs, PCBs, DDTs and mirex, and 17β-estradiol (Verboven et al., 2010). Although plasma testosterone levels did not correlate with blood levels of these compounds in this colony (Verreault et al., 2006), plasma progesterone levels were positively correlated.

2.2.3. Reproduction and genotoxicity

Studying the effects of POPs and Hg on reproduction is particularly important in the suite of biological effects as negative impacts on reproduction can alter a population's reproductive rate in several ways. In Arctic birds, this can include the most common direct measures of reproduction including propensity to breed, breeding onset (i.e., timing of breeding), breeding productivity (i.e., clutch size, egg development), and breeding success (i.e., nest success, chicks fledged). POPs and Hg can also affect other facets of reproduction, such as sex bias of clutches and lack of return to the breeding colony in the following year that can have further effects. Although the number of studies on Arctic avifauna is limited, there is a large body of work examining the impacts of POPs and Hg on avian reproduction, which suggests that exposure to these contaminants can lead to aberrant reproductive behavior, reduced clutch size, increased rates of embryonic deformity and mortality, and reduced hatchability (Thompson, 1996; Wolfe et al., 1998; Scheuhammer et al., 2011, 2015).

Most studies of the biological effects of Hg and POPs on reproduction in Arctic birds have focused on a few species that are relatively easy to study during the breeding season. This includes species with high levels of POPs and Hg (e.g., glaucous gull) and species commonly found to have lower levels of these contaminants (e.g., common eider). There are species for which reported levels are again much higher than for those most commonly studied species (e.g., ivory gull), but biological effect studies on such species are difficult if not impossible in many regions due to their ecology (including limited access to breeding sites and low numbers). In general, Arctic avian studies on POPs and Hg have focused mostly on marine birds. There are some data available for insectivorous passerines, but concentrations in those terrestrial avian species that have been studied are low compared to aquatic high-trophic level species (Scheuhammer et al., 2011).

Breeding propensity refers to whether an individual undertakes a breeding attempt in a given year. As many Arctic bird species are relatively long-lived an individual in poor condition may forego breeding, and so propensity can be indicative of an individual's ability to reach breeding condition (Goutte et al., 2011, 2015). Tartu et al. (2013) found that black-legged kittiwakes from Svalbard that had higher blood concentrations of total Hg were more likely to avoid breeding (and have abnormal reproductive hormonal responses). In contrast, recent work in Hudson Bay, Canada, showed that the propensity for eider duck to breed was unrelated to blood Hg concentration on arrival at the breeding colony (Provencher et al., 2017).

Onset of breeding refers to when an individual initiates breeding, which can differ by species, but in general signals that an individual has reproduced that year. Onset can be highly variable, and in Arctic birds where the breeding season is limited by weather and resources there is evidence that those who initiate breeding earlier are often more successful (Descamps et al., 2011). Tartu et al. (2013) found that Hg concentrations had no relationship with lay date in black-legged

kittiwakes from Svalbard. Similarly, there was no relationship found between blood total Hg concentrations and lay date in common eider from northern Hudson Bay, Canada (Provencher et al., 2016).

Effects can also be determined from the development of eggs and chicks. In a laboratory experiment, Braune et al. (2012) found that increased MeHg concentrations lead to decreased survival of eggs of both thick-billed murres (*Uria lomvia*) and Arctic terns (*Sterna paradisaea*). Other Arctic bird species that have been studied are Canada goose (*Branta canadensis*) and sandhill crane (*Grus canadensis*). Canada geese were found to have a low sensitivity to MeHg in eggs, with an LC50 of 1 μg/g or above (Heinz et al., 2009). Sandhill cranes were found to have a medium sensitivity, with an LC50 of 0.25–1 μg/g (Heinz et al., 2009). The two raptor species included in that study (American kestrel *Falco sparverius* and osprey *Pandion haliaetus*) showed a high sensitivity to MeHg, with an LC50 when injected of <0.25 μg/g (Heinz et al., 2009). This suggests that Arctic birds of prey may also show sensitivity in egg survival when exposed to high levels of Hg. Tartu et al. (2013) found no relationship between total Hg and clutch size or breeding success in black-legged kittiwakes from Svalbard.

Erikstad et al. (2011) found the body mass of male chicks to be negatively correlated with maternal levels of OCs, but found no relationship for female chicks. This study also showed that both condition and maternal OC concentrations can influence the sex ratio in clutches; in females with high OC levels, there was an overall skew sex distribution in clutches towards male offspring, which was most apparent in birds with poor body condition. Provencher et al. (2016) found a significant positive relationship between Arctic-breeding female common eider arrival condition and blood Hg concentrations. This finding is counter to previous findings in eiders and other bird species where higher Hg burdens are associated with poorer condition. This may be related to recent feeding bouts leading to an increase in condition, while long-term Hg accumulation leads to negative effects over the longer term (Provencher et al., 2016). Studies examining survival rates (resighting at the colony in subsequent years) and contaminants, show variable results. Previous work on king eiders (*Somateria spectabilis*) in north central Canada (Wayland et al., 2008) established a link between individual blood contaminant concentrations and survival, while other studies on the return of Arctic-breeding birds to colonies showed no link between Hg and POPs with return rates (Bustnes et al., 2006). Similarly, no relationship was found in eiders between blood Hg concentrations and return rates (Provencher et al., 2017). These mixed results on the effects of POPs and Hg on return rates to colonies suggest survival is influenced by several variables including exposure to environmental contaminants (Goutte et al., 2015).

Although indirect, a recent study by Blevin et al. (2014) has shown that higher POP levels can have a negative association with several components of integument coloration, e.g. saturation of eye-ring, gapes and tongue, suggesting that POPs could disrupt coloration of labile integuments in female kittiwakes. Many studies suggest that coloration is an indicator of condition, which suggests that POPs may also be altering breeding condition.

Work has shown that contaminants in association with other stressors may have cumulative effects on health and reproduction in birds (Bustnes et al., 2015). In addition, experiments on common eiders in the Canadian Arctic have shown that Hg exposure had no significant effect on reproduction, while parasites influenced breeding, suggesting that cumulative effects are likely to be more of a concern in species with higher exposure rates (Provencher et al., 2017).

A common theme throughout the studies reviewed above is that age and sex may also play a role in how contaminants affect reproduction (see Costantini et al., 2014). It is also important to note that due to fasting during incubation studies, female eiders had higher levels of lipid-soluble organochlorines (Bustnes et al., 2010a). As a result, reproduction in females may inherently increase the mobilization of some OHCs, and increase the potential effects of these POPs in females during this period. Increased POP concentrations during reproduction are also of concern because they often coincide with poor body condition and weakened immune systems.

Since the last AMAP effects reports (Letcher et al., 2010; Dietz et al., 2013a), at least two studies have reported on genotoxicity in Arctic birds (Blevin et al., 2016; Fenstad et al., 2014). Lipophilic POPs are released from the fat reserves of birds during fasting, causing increased blood concentrations. Thus, POPs represent a potential anthropogenic stressor during bird fasting periods. Fenstad et al. (2014) reported on PCB and DNA double strand-breaks in female common eiders during the eider incubation period in the High Arctic. In 2008 and 2009, nine POPs and DNA-FTM were sought in blood samples at day 5 of the incubation period, and then again in the same individuals at day 20. During the incubation period, eider body mass decreased by 21–24%, whereas POP levels increased by 148–639%. The DNA-FTM increased by 61–67% (being proportional to the increase in double strand-breaks). At day 5, but not day 20, DNA-FTM was positively correlated with most POPs investigated. The increase in DNA-FTM was positively correlated with the decrease in body mass during incubation. The authors suggested that fasting stress (body mass loss) decreased DNA integrity and that stress caused by fasting appeared to override the additional stress caused by concurrent increase in the levels of the POPs. The study concluded that blood levels of POPs in the Svalbard eiders were relatively low, and that additive and/or synergistic genotoxic effects of fasting stress and POP exposure may occur in populations with higher POP levels. In addition to this, Blevin et al. (2016) found that exposure to oxychlordane was associated with telomeres lengths (shorter) in kittiwakes from Svalbard.

Haarr et al. (2018) measured DNA damage in lymphocytes from six Arctic seabird species from Kongsfjorden, Svalbard, using the comet assay. The species studied were common eider ($n = 12$), black-legged kittiwake ($n = 15$), black guillemot (*Cepphus grylle*, $n = 10$), Arctic skua (*Stercorarius parasiticus*, $n = 10$), glaucous gull ($n = 14$), and great skua ($n = 4$). Fresh lymphocytes were isolated from whole blood sampled during the incubation/early chick-rearing period. The sensitivity of lymphocytes from each individual to oxidative stress was assessed in vitro through exposure to hydrogen peroxide, and the ability to repair induced damage was assessed by allowing exposed lymphocytes to recover for 1 h. Baseline DNA damage was low and not significantly different for lymphocytes of the five species: average tail intensity was 1.7% (common eider), 1.7% (black-legged kittiwake), 0.4% (black guillemot), 3.9% (Arctic skua), and 1.5% (glaucous gull). Great skua had a significantly higher baseline than the other species at 8.6%, but only four individuals were sampled for this species. The lowest contaminant concentrations were found in common eider (ΣOHCs 3.4 ng/g ww), with higher concentrations in black guillemot (35 ng/g ww), kittiwake (33 ng/g ww), and Arctic skua (36 ng/g ww), and highest concentrations in top predators, glaucous gull (255 ng/g ww) and great skua (515 ng/g ww). They found no significant relationship between DNA strand breaks and contaminant concentrations in lymphocytes for any of the species or POPs studied, which suggested that avian lymphocytes are robust cells, apparently unaffected by contaminant exposure. Another alternative explanation was that the contaminant concentrations in Kongsfjorden are too low for genotoxic effects to occur. Exposure to oxidative stress caused increased DNA damage in lymphocytes from all species: average tail intensity was 39% (common eider), 47% (black-legged kittiwake), 26% (black guillemot), 47% (Arctic skua), 40% (glaucous gull) and 27% (great skua). The differences were not significant and there was no indication of reduced DNA damage after 1 h of recovery in buffer to allow repair. On the contrary, kittiwake lymphocytes showed a significant increase in DNA damage 1 h after exposure. El-Bibany et al. (2014) showed that DNA damage could continue to increase for up to 6 h after exposure to H_2O_2 and that complete recovery was not evident until 24 h after exposure.

2.2.4. Immunology

There are two main components of immunity that are traditionally studied: cell-mediated immunity and humoral immunity. Cell-

mediated immunity refers to immune responses that do not involve antibodies; this includes activation of phagocytes, lymphocytes and cytokines when exposed to an antigen (Fig. 2). These processes usually involve cells or proteins that destroy or attack pathogens within the body. Humoral immunity is the antibody-mediated immune system, which consists of macromolecules that are found in extracellular fluids. POPs and Hg have both been shown to affect cell-mediated and humoral immunity functions (Corsini et al., 2014). However, there are few studies that have tested this directly in Arctic marine and terrestrial birds.

In an examination of cell-mediated immunity function effects, feeding experiments with captive adult and nestling American kestrels fed environmentally relevant levels of MeHg exhibited immunosuppression under both low and high MeHg doses (Fallacara et al., 2011a, 2011b). Three treatment groups of adults were given MeHg for 13 weeks: control (0), low (0.6 μg/g dw) and high (3.9 μg/g dw). Adult kestrels in the low and high exposure group had lower responses to phytohemagglutinin skin-swelling assays, and a depletion of T cell-dependent splenic lymphoid tissue (Fallacara et al., 2011a). The high exposure group also exhibited an increase in absolute heterophil counts, elevated heterophil to lymphocyte ratios, and higher total white blood cell counts in adults (Fallacara et al., 2011a). American kestrel nestlings exposed in the same way for up to 18 days post-hatch showed suppressed cell-mediated immunity to the phytohemagglutinin skin-swelling assay at day 11. Nestlings in the high dose group also showed lymphoid depletion and a lack of macrophage activity in the thymus. In the same study MeHg doses did not alter B cell-dependent histological variables in American kestrels (Fallacara et al., 2011b). Overall, the authors suggested that their findings demonstrate that adult kestrels are more sensitive to immunotoxic effects of environmentally relevant levels of MeHg than reproductive effects.

Slightly more work has been done to study humoral immunity function effects in relation to OHCs and Hg in Arctic marine birds, although the results show mixed findings. In captive adult American kestrels the secondary response to the sheep red blood cell hemagglutination assay showed no difference between the MeHg exposure groups (control, low and high), although the low exposure group showed suppressed primary immune responses to the sheep red blood cell hemagglutination assay (Fallacara et al., 2011a). In captive nestling American kestrels MeHg did not have any detectable effect on antibody- mediated immune function when exposed to the sheep red blood cell hemagglutinin assay (Fallacara et al., 2011b).

Work has also been undertaken in natural settings. A study examining immunity metrics in both sexes of great skua nesting in the Shetland Islands, Iceland, and Bjørnøya found no significant relationship between immunoglobulin Y (IgY) and OCs or PBDEs (Bourgeon et al., 2012). Provencher et al. (2017) also found no relationship between levels of IgY and blood Hg concentration in common eiders in northern Canada. Similarly, no relationship was found between concentrations of POPs – HCB, oxychlordane, *p,p′*-DDE, PCBs and PBDEs – and levels of IgY or the primary response of IgY to tetanus toxoid in black-legged kittiwakes from Hornøya, Norway (Sagerup et al., 2014). Although, in the same study, Sagerup et al. (2014) did find significant correlations between the IgY response to tetanus toxoid and several POPs for Atlantic puffins (*Fratercula arctica*). The relationships had variable directions and the explanatory values were quite low. Male puffins had a significant negative correlation between circulating levels of IgY and CB170 and CB180, while IgY levels in females were positively correlated with HCB, oxychlordane, CB28, CB99, CB170 and CB180. The authors suggested that the opposing correlation directions for males and females may indicate gender-specific differences in immune responses. Of particular note, is that studies of POPs and Hg in Arctic birds often show large interannual differences (Bustnes et al., 2004), as well as significant differences between the sexes (Sagerup et al., 2014). This demonstrates that although POPs and Hg may affect some immune responses, any given response may be heterogeneous in nature and vary with season, time and sex.

2.2.5. Skeletal system

Since the last AMAP effects reports (Letcher et al., 2010; Dietz et al., 2013a), no new studies have reported on the effects of OHC and Hg exposure on the skeletal system in Arctic marine and freshwater birds.

2.2.6. Histopathology

Previous AMAP reports could not summarize histological studies on Arctic bird species because none existed at the time (Letcher et al., 2010; Dietz et al., 2013a). Since then, there have been two new histopathological studies on glaucous gull, one focused on thyroid glands (Sonne et al., 2010b) and one on multiple organs (Sonne et al., 2013c). In the latter, the histology of liver, kidney and thyroid tissues was studied in 10 gulls from Svalbard in 2011, with reported hepatic PCB concentrations ranging from 150 to 2820 ng/g ww. All specimens showed histological changes, including kidney lesions (70%) and thyroid gland changes (50%). POP concentrations were non-significantly higher in individuals with various lesions and histopathological changes, which were all similar to those found in laboratory studies and wild polar bears. In their study on thyroid gland lesions, Sonne et al. (2010b) examined 10 adult gulls from Bjørnøya in the Norwegian Arctic during their incubation period, and reported blood plasma PCB concentrations ranging from 186 to 1027 ng/g ww. High densities of small follicles and follicular epithelial cell proliferations (70%) were found, as well as focal thyroiditis and nodular hyperplasia (20%). Such changes may affect hypothalamic-pituitary-thyroid axis functioning, thus possibly affecting energy metabolism in adults, and cell differentiation, growth and development of hatched chicks. The authors suggested that POP exposure may be a co-factor in the development of organ alterations in glaucous gulls, but highlighted the need for further investigation into the natural variance of tissue pathology in this species.

2.2.7. Neurology and behavior

There have been a few new reports on contaminants in relation to neurology and behavior in Arctic birds since the last AMAP effects reports (Letcher et al., 2010; Dietz et al., 2013a). Life-history theory predicts that long-lived organisms should reduce parental effort under inclement environmental conditions in order to favor long-term survival. Seabirds are long-lived and feed higher in the marine food web and thus are often exposed to higher levels of environmental contaminants such as Hg, which can cause disrupted parental behavior in birds. Parental behavior is governed by two key hormones in birds: CORT and prolactin. Any disruption of these hormones may alter the ability of an individual to adjust parental behavior to environmental conditions. Tartu et al. (2016) recently reported on the relationships between blood Hg concentrations, plasma prolactin and reproductive performance in Arctic black-legged kittiwakes. There was a negative relationship between plasma initial prolactin and blood Hg concentrations in males. Hg concentration was negatively related to breeding success in chick-rearing males. To study the effect of a chronic increase in CORT levels on the Hg-prolactin relationship, the stress of the birds was increased experimentally with CORT pellet implantation. Adding CORT did not change the Hg-prolactin relationship. Hatching success was significantly lower in CORT-implanted males than in controls, and breeding success was not reduced in CORT-implanted male kittiwakes with high levels of blood Hg. It was suggested that Hg may impair reproductive performance through a disruption in prolactin secretion.

Hargreaves and Whiteside (2010) addressed a hypothesis to explain the global decline in shorebirds, which is of particular concern in the Arctic. Elemental contaminants were studied in three biparental shorebird species nesting in Nunavut, Canada: ruddy turnstones (*Arenaria interpres*), black-bellied plovers (*Pluvialis squatarola*) and semipalmated plovers (*Charadrius semipalmatus*). Blood, feathers and eggs were analyzed for Hg as well as for arsenic, beryllium, cadmium, cobalt, chromium, copper, iron, manganese, molybdenum, nickel, lead, antimony, selenium, thallium, vanadium and zinc. Non-essential elements were found at lower concentrations than essential elements, with the

exception of Hg. Maximum Hg levels in blood approached those associated with toxicological effects in other bird species, but other elements were well below known toxicological thresholds. Reproductive success was negatively correlated with paternal Hg and maternal lead, although these effects were generally weak and varied among tissues. Element levels were positively correlated within pairs for blood-Hg (turnstones) and feather nickel and chromium (semipalmated plovers); concentrations in eggs and maternal blood were never correlated. The authors concluded that there was little evidence supporting a link between exposure to elements and population declines in these species.

2.2.8. Bioenergetics

Most work on Arctic bird bioenergetics was carried out prior to the last OHC assessment by Letcher et al. (2010). In this review based on previous findings it was suggested that circulating thyroid hormone homeostasis may be perturbed in highly OHC-exposed glaucous gulls (males) breeding on Bjørnøya (Verreault et al., 2004, 2007). In males and females combined, negative associations were found between basal metabolic rate (BMR) and plasma concentrations of ΣPCBs, ΣDDTs and particularly ΣCHLs, thus suggesting potentially altered functions of the basal metabolism. However, levels of free and total T4 and T3 were not significantly associated with the variation in BMR or concentrations of any of the OHCs determined. A companion study by Verboven et al. (2009) using the same colonies on Bjørnøya showed that the nest temperature of glaucous gull males and females was negatively correlated with the concentrations of certain OHCs, BFRs (PBDEs and HBCD) and OH-PCB metabolites in plasma of the incubating parent. To test the parental control of incubation conditions in relation to OHC exposure, the energetic cost of incubation was augmented by artificially increasing clutch size from two to four eggs using dummy eggs. Clutch enlargement in glaucous gulls was followed by a decrease in nest temperature, although this decrease was not associated with plasma OHC concentrations.

Seasonal changes in body fatness are likely to influence dynamics of lipophilic POPs in Arctic seabirds. For example, circulating CB153 and *p*, *p*′-DDE increased four and eight-fold in female common eiders from Svalbard, that may loose a third or more of their body mass during nesting (Bustnes et al., 2010b). Body condition has also been negatively related to plasma concentrations of lipophilic POPs in non-breeding black legged kittiwakes from Svalbard (Tartu et al., 2014b). An experimental study on herring gulls demonstrated that concentrations of lipophilic POPs and their metabolites (OH-PCBs and $MeSO_2$-PCB) in liver, brain and blood increased 2–3 fold during a period of reduced food intake when the animals lost on average 11% of their body mass (Routti et al., 2013). In addition, Blevin et al. (2017) showed a negative relationship between the sum of all detected chlordanes (∑CHLs) and metabolic rate (MR) in black-legged kittiwakes on Svalbard.

2.2.9. Clinical chemistry

Analyzing blood plasma clinical-chemical parameters (BCCPs) gives a holistic evaluation of the biochemical, metabolic, and endocrine status of the vertebrate organism. BCCPs have been proven to serve as a minimally-invasive strategy to quantify adverse health effects of OHCs in free-ranging birds (Sonne et al., 2010b, 2012b, 2013d). BCCPs are usually used as biomarkers of health and function of different organ systems in mammals and birds (Sonne, 2010; Sonne et al., 2012b). Other factors such as feeding behavior and food items, time since last feeding, infectious diseases, dehydration and age are other factors that influence BCCPs (Thrall et al., 2004; Candido et al., 2011; Harr, 2012; Sonne et al., 2012b; López et al., 2015; Peng et al., 2015).

Since the last AMAP reports (Letcher et al., 2010; Dietz et al., 2013a), three new studies on BCCPs in Arctic avian wildlife, including top avian predators such as great skua, northern goshawk (*Accipiter gentilis*), white-tailed eagle, and golden eagle (*Aquila chrysaetos*), have focused on OHCs in the marine environment of the North Atlantic (Sonne et al., 2010c, 2012b, 2013d). Concentrations of most BCCPs were positively or negatively associated with those for OHCs. While renal and liver functioning may be affected by different compounds, all three studies showed consistently increased alanine transferase, albumin, and total protein as a result of OHC exposure, which was shown to explain 10.6% of the total observed BCCP variation. In one study, Sonne et al. (2013d) compared BCCPs in birds from three geographically distinct North Atlantic great skua colonies. Birds from these sites bioaccumulate different OHC concentrations and this made it possible to compare great skua BCCP regulation under different exposure scenarios. PCBs, DDTs, chlordanes, HCB, HCHs, Mirex and PBDEs, and 19 BCCPs were sought in 114 adult great skuas sampled during summer 2009 in North Atlantic colonies at Bjørnøya, Iceland and the Shetland Islands. Specimens from Bjørnøya had the highest blood plasma concentrations of all contaminant groups followed by Iceland and the Shetland Island birds, respectively. Most of the 19 BCCPs followed the pattern of colony differences found for the OHCs with Bjørnøya having the greatest concentrations of BCCPs. However, seven BCCPs, the three liver enzymes (alkaline phosphatase, alanine transaminase, gamma glutamyl transferase), as well as bile acids, cholesterol, sodium and potassium concentrations did not differ among colonies. Analyses of combined colony data showed that the blood plasma concentration of alanine transaminase and gamma glutamyl transferase increased with increasing concentrations of PBDEs and HCHs, HCB and chlordanes, respectively. Based on these results the authors suggested that liver and renal functions could be negatively affected by different OHCs. However, it is not clear whether the colony-specific BCCP concentrations and their relationship to OHC exposure reflect health effects that could have an overall impact on the population via reduced survival and reproduction.

2.3. Marine and freshwater fish

Fish can accumulate high concentrations of OHCs and Hg and are an important vector of these contaminants to humans and wildlife. Compared to mammals and birds, little is known about contaminant impacts in fish, including the large confounding factor of Arctic climate change. Since the last AMAP effects reports on Hg and OHCs (Letcher et al., 2010; Dietz et al., 2013a), for Arctic marine and freshwater fish there continues to be limited information on OHC and Hg related effects. Mercury has an extremely complex biogeochemical cycle with many processes affected by climate and it appears that temporal trends in Hg concentration in char may be recording changes in inputs of Hg (to lakes) and in fish there have been no new studies reported on the effects of contaminant exposure on endocrinology, immunology, neurology and behavior, or clinical chemistry. However, there have been some recent reports on Arctic fish effects on bioenergetics, vitamins and oxidative stress, reproduction, genotoxicity, the skeletal system and histology. The previous sections on birds and mammals were subdivided based on types of effects. Given the sparse amount of recent data on fish, this section is species and/or Arctic region based. The focus is on biological effects of PCBs and Hg on Arctic char (*Salvelinus alpinus*) from lakes of Bjørnøya (Svalbard, Norway) and Cornwallis Island (Nunavut, Canada), respectively. The section concludes with (sparse) information on Greenland shark (*Somniosus microcepalus*), sculpins, and other fish taxa.

2.3.1. Arctic char

Arctic char are widely distributed in the Arctic, and can be an important food source for indigenous peoples. In Canada, the federally-funded Northern Contaminants Program has supported extensive efforts to measure contaminants in Arctic char. Anadromous (sea-run) Arctic char are relatively low in contaminants and are promoted as a nutritious food source by public health authorities. In contrast, landlocked Arctic char (restricted to lakes and connecting streams) are relatively high in contaminants, especially Hg (Swanson et al., 2011). In an overview of the peer-reviewed literature, Drevnick (2012) reported that 30% (12 of 40) of landlocked populations sampled in northern Canada and

Greenland exceed Hg concentrations known to cause toxicity (in fish) and thus are at risk from effects of Hg. For any given population, Hg concentrations increase with age and size, and in some lakes a large increase in Hg concentrations occurs with a switch, in the biggest char, from invertivory to piscivory. Among Arctic lakes, concentrations of Hg in Arctic char show a positive correlation with watershed-to-lake area ratio (Gantner et al., 2010a), indicating that the relative size of the 'collection basin' for wet and dry atmospheric Hg deposition determines the level of contamination. The Northern Contaminants Program uses annual sampling of landlocked Arctic char from lakes on Cornwallis Island and Ellesmere Island for tracking temporal changes in inputs of atmospheric contaminants. As expected, concentrations of legacy OHCs are declining but replacements (e.g., bis(2,4,6- tribromophenoxy) ethane) for banned BFRs such as PBDEs are increasing (Muir et al., 2014). Concentrations of Hg in landlocked Arctic char show a significant downward trend since 2005. Interestingly though, peaks are evident throughout the record in association with warm summer temperatures, which is also seen in a lake in southwest Greenland (Rigét et al., 2010), and Pacific air masses. Mercury has an extremely complex biogeochemical cycle with many processes affected by climate and it appears that temporal trends in Hg concentration in char may be recording changes in inputs of Hg (to lakes) and in climate.

2.3.2. Biological effects of Hg and other metals on Arctic char from the Canadian Arctic

From a climate change and bioenergetics perspective for fish, Stern et al. (2012) summarized the literature on how climate change influences Arctic Hg levels. This included the finding that long-term warming of freshwaters is likely to alter fish growth rates (Reist et al., 2006a) and hence affect their bioaccumulation, resulting in lower Hg concentrations in fish with higher growth rates (Simoneau et al., 2005). Also, that cold-adapted species such as Arctic char and lake trout grow less efficiently in warmer waters (Reist et al., 2006a), which could result in higher Hg concentrations. Temperature-induced metabolic stress in fish may also enhance Hg bioaccumulation (Reist et al., 2006b). A multi-year study of Arctic char in a High Arctic lake revealed that fish were under greater metabolic stress and had severe glycogen depletion near the end of an abnormally warm summer compared to two colder years (Reist et al., 2006b). However, Stern et al. (2012) concluded that further research is required to determine the effect of temperature stress on Hg bioaccumulation in cold- adapted fish species.

In order to determine the potential toxic effects of Hg, landlocked Arctic char ($n = 114$) were sampled in 2011 and 2012 from four lakes in the Canadian High Arctic that span a gradient of Hg contamination (Drevnick, 2012, 2013; Barst et al., 2016). Individual fish from these lakes (Small, 9-Mile, North, Amituk), located on Cornwallis Island, were collected in conjunction with routine sampling for contaminant monitoring (Muir et al., 2012, 2013). Total Hg and stable isotopes ($\delta^{15/14}N$, $\delta^{13/12}C$) were measured in muscle. Bulk liver tissues were analyzed for total Hg, Hg speciation, and Se. To investigate how Hg and Se were distributed at the subcellular level, char liver tissues from Small Lake (low Hg) and Amituk Lake (high Hg) were subject to a trace element partitioning procedure based on differential centrifugation. This yielded six operationally defined fractions which were then analyzed for total Hg and Se. Fractions were assigned to one of two groups, including a potentially sensitive compartment (mitochondria and heat-denatured proteins including enzymes and microsomes and lysosomes) and a detoxified compartment (peptides and heat-stable proteins including metallothionein + granule-like concretions) (Wallace et al., 2003; Giguère et al., 2006; Rosabal et al., 2012, 2015). Liver tissues were preserved for histological analysis. Reproductive status was assessed using the gonadosomatic index and (for females only) egg quality (size) and quantity. General (body) condition was determined according to relative weight (LeCren, 1951), with the denominator (w′) determined from a regression of length versus weight with data from all four lakes for char sampled (as part of routine sampling) from 2009 to 2014.

Mean total Hg concentrations in muscle tissue were greatest in char from Amituk Lake, intermediate in char from North Lake and 9-Mile Lake, and lowest in char from Small Lake. $\delta^{15/14}N$ values followed a similar trend. Total Hg concentrations in liver were two to five times greater than in muscle, with a maximum of 6.5 μg/g ww for an individual from Amituk Lake. For all livers, the fraction of MeHg ranged from 51% to 90% of total Hg, and increased exponentially with $\delta^{15/14}N$ values, which is consistent with studies demonstrating that food web structure plays an important role in determining the level of Hg contamination in landlocked Arctic char (Muir et al., 2005; Gantner et al., 2010a, 2010b; Lescord et al., 2015). In the same study, Se concentrations in the liver samples ranged from 0.9 to 6.5 μg/g ww. Concentrations of hepatic Se were significantly higher in char from Amituk Lake than in char from the remaining study lakes ($p < 0.0001$) and were positively correlated with total Hg. The molar concentration of Se was greater than total Hg (mean molar ratio Hg:Se = 0.15) in all char livers, although this value increased with increasing Hg concentration to a maximum of 0.7 in a fish from Amituk Lake. Hg concentrations were significantly higher in isolated fractions of Amituk char than in char from Small Lake, which was consistent with the results of bulk liver analysis. Despite the higher Hg concentrations in subcellular fractions prepared from Amituk livers, Hg was distributed similarly among char liver fractions from both lakes. The sensitive compartments contributed 73% and 61% of the contributions of total Hg in Small and Amituk livers. This suggests that at low (Small Lake) and high (Amituk Lake) concentrations, Hg is not effectively detoxified in the livers of these fish. The remaining Hg was found in the detoxified compartments, which comprised 10% and 19% of the total Hg contributions of Small and Amituk char, respectively. Almost all of the Hg in the detoxified compartments was associated with the heat-stable protein fraction, presumably containing metallothionein, whereas very little was found in the granule- like fraction. In the potentially sensitive compartments, Hg accumulated mainly in the mitochondria and heat-denatured protein fraction containing enzymes. Selenium was distributed similarly among fractions, suggesting an interaction between the two elements.

Histological investigation revealed hepatic fibrosis in the perisinusoidal region, predominately in the livers of Amituk Lake char. A significantly greater number of individuals from Amituk Lake (83%) exhibited this abnormality than individuals from the other study lakes. Evidence of fibrosis was also found in individuals from 9-Mile (29%) and North Lake (27%). None of the livers from Small Lake char presented this abnormality. Arctic char are commonly hosts to cestode parasites, which have been shown to increase in number in piscivorous char (Frandsen et al., 1989). These parasites may cross the intestinal wall, and enter the liver and other organs, resulting in fibrosis and visceral adhesions (Frandsen et al., 1989; Hammar, 2000). Although Hg may have resulted in the observed fibrosis the role of parasites cannot be excluded as these may be particularly abundant in the char sampled from Amituk Lake. Future work is needed to decouple the effects of parasites and non-essential metals such as Hg.

There was no relationship between whether ovaries or testes were developed (i.e. maturation index) and total Hg. In terms of body size, as char grow bigger, they have proportionally bigger gonads, but also more Hg. If the 'effect' of body size on gonadosomatic index is accounted for, the results indicate that total Hg is not related to gonadosomatic index. For females with developed ovaries, egg number and size (diameter) increased with body size. Correcting for body size, by calculating relative fecundity (number of eggs per 100 g of body weight) and relative egg diameter (egg diameter/fork length), yields data that show possible effects of Hg. Total Hg concentration in muscle is negatively related to relative fecundity and positively related to relative egg diameter. Venne and Magnan (1989) predicted that, for a female char with a limited energy budget, "the first response to an additional stress would involve a decrease of the number of eggs and an increase of their diameter

without affecting the gonadosomatic index". Higher probability of larval survival (owing to an increase in egg size) is balanced by a reduction in the number of eggs. The results thus indicate that Hg may be exerting effects on reproduction indirectly, that is, energy used by the liver for tissue repair (see above) may result in females altering their egg production.

2.3.3. Biological effects of PCBs on Arctic char from Bjørnøya lakes

Lake Ellasjøen and other (reference) lakes on Bjørnøya, the southernmost island of the Svalbard archipelago in the Barents Sea, have been used to document the biotransport of OHCs from the marine environment to land (which includes lakes that Arctic char inhabit), via seabirds. Bjørnøya is a site of global significance for bird conservation (BirdLife International, 2018) with nesting colonies of threatened bird species that number in the tens of thousands. In the pre-2010 period, Evenset et al. (2004, 2007) used nitrogen isotopes ($\delta^{15}N$) to trace the input of seabird guano into Ellasjøen and determined that guano accounts for the majority (>80%) of OHC inputs to the lake. Wiseman et al. (2011) and Neerland (2016), have studied the impacts of this novel contaminant pathway to lakes on the health of fish. Wiseman et al. (2011) examined the expression of selected protein markers of exposure and effects between landlocked Arctic char from highly-contaminated Lake Ellasjøen and reference Lake Øyangen at Bjørnøya. Fieldwork was conducted in 2002 and samples were collected from a limited study group of three immature male char from each lake. The mean concentration of ΣPCBs in liver of char in Ellasjøen (281 ng/g ww) was about 25-times greater than in Øyangen (11.3 ng/g ww). Likewise, liver expression of cytochrome P4501A (CYP1A), a protein induced in Phase I metabolism of ligands of the aryl hydrocarbon receptor (including PCBs), was about 50-times greater in char from Ellasjøen than from Øyangen. CYP1A is considered a marker of exposure (gene/protein expression), and the molecular response (detoxification or activation of PCBs) and biological consequences are unknown (for these char). Expression of heat-shock protein 70 (hsp70) (brain, but not liver) and the glucocorticoid receptor (liver) were also greater in char from Ellasjøen than from Øyangen. No difference was reported in (body) condition of char between the two lakes.

Neerland (2016) recently reported on DNA lesions, measured as DNA double strand-breaks in landlocked Arctic char at Bjørnøya (n = 39 individuals, 18 from exposed Lake Ellasjøen and 21 from control Lake Laksvatn). Concentrations of ΣOCs were about 40-times greater in char from Ellasjøen compared to char from Laksvatn, and char from Lake Ellasjøen had a significantly higher frequency of DNA double strand-breaks compared to char from Lake Laksvatn. Furthermore, the difference was significantly positively correlated with the levels of OCs in the fish.

2.3.4. Greenland shark

High levels of OHCs and Hg have been detected in Greenland shark from the Canadian Arctic (Baffin Island) and Iceland (Fisk et al., 2002; Strid et al., 2007). Little is known about Greenland shark ecology but it has been suggested that they could reach 100 years of age (Hansen, 1963) and that their diet consists of everything from invertebrates to fish and marine mammals (Compagno, 1984; Fisk et al., 2002; Yano et al., 2007; Lucas and Natanson, 2010). Their migratory range appears to be relatively limited, as reported for the Greenland sharks tagged at Svalbard that appear to remain in the waters around Svalbard (Fisk et al., 2002). A recent study on Greenland shark sampled outside Svalbard indicates that marine mammals are a common part of their diet (Leclerc et al., 2012). Both their great age and their consumption of high trophic level species can explain the high levels of OHCs and Hg documented in the sharks.

Female and male Greenland sharks (n = 43) were caught by longlines in the Kongsfjorden of Svalbard in 2008 and 2009 (Molde et al., 2013). Plasma samples were collected for contaminant and vitamin analysis to examine the potential impact of OHCs on vitamin A (retinol) and its precursor retinyl palmitate, and vitamin E (α-tocopherol) homeostasis. DDTs were the dominant contaminant group in the plasma (ΣDDTs: 8069 ± 8793 ng/g lw) followed by PCBs (ΣPCBs: 5766 ± 3716 ng/g lw) and chlordanes (ΣCHLs: 1551 ± 1152 ng/g lw). PBDEs were detected only in a few individuals. Multivariate correlation analyses (principal component analysis) indicated negative associations between POPs and plasma levels of vitamin A and retinyl palmitate, while a positive association was found between POPs and plasma levels of vitamin E. Follow-up analyses of the vitamin A model using multivariate regression analysis indicated that the strongest negative associations between OHCs and vitamin A were between vitamin A and the dioxin-like PCBs, CB118 and CB156/CB171, as well as the non-dioxin-like PCBs, CB99 and CB128. In these models, covariates such as lipid percentage, hepatosomatic index and the animal's condition factor were taken into account. As for vitamin A, PCBs, as well as chlordanes, were also the dominating compounds found to correlate with retinyl palmitate, while PCBs exclusively correlated with vitamin E. Vitamin A, retinol palmitate and vitamin E were not associated with gut content mass. Although the reported associations do not necessarily reflect a cause-effect relationship, the high levels of OHCs and the relationships with vitamin levels are of concern due to the vital role of vitamins in development, embryogenesis, reproduction and immune function.

The Canadian Arctic Contaminants Assessment Report on Hg in Canada's north (Chetelat and Braune et al., 2012) identified Greenland shark as the single marine fish species (in Canada's Arctic) with Hg concentrations in excess of values known from laboratory and field studies to cause "changes in biochemical processes, damage to cells and tissues, and reduced reproduction in fish" (Sandheinrich and Wiener, 2011). As such, the authors stated that studies are warranted to investigate toxic effects of Hg on Greenland sharks and other large predatory marine fishes. No studies have been conducted to date.

2.3.5. Sculpin

Generally, high site fidelity of sculpin make this superfamily of fishes (Cottoidea) an attractive indicator of ecosystem health, especially in relation to point sources of pollution. Kuzyk et al. (2005) used shorthorn sculpin (*Myoxocephalus scorpius*) to understand exposure to and ecological risks in benthic fishes from PCBs released from a military installation to Saglek Bay, Labrador, Canada. Thirty-five sculpins were collected from four zones of contamination and a reference site and analyzed for PCBs and biological endpoints, including condition factor, lipid content, hepatosomatic index, and ethoxyresorufin-*O*-deethylase (EROD) activity. ΣPCB concentrations in whole carcasses (excluding liver) were in the range 5.1–6920 ng/g ww. EROD activity, a measure of CYP1A induction, was positively correlated to ΣPCB concentration, and was 25-times greater in the most contaminated sculpin compared to those from the reference site. Other biological endpoints were not related to ΣPCB concentrations or EROD activity.

Sculpin have also begun to be included in Arctic assessments of environmental contaminant effects on organ histology. Several studies have now been published linking histopathological parameters, parasites and elemental tissue concentrations (Dang et al., 2017; Dang et al., 2018; Dang et al., 2019; Kaarsholm et al., 2019; Nørregaard et al., 2018; Sonne et al., 2014c; Verland et al., 2019). In Sonne et al. (2014c), eleven different elements were sought together with the histopathological investigations. Chronic lesions were observed in liver and gill tissue of common sculpins and individuals with hepatic cell infiltrates had the highest concentrations of most elements. For 20% of the sculpins, Hg concentrations were above the LOED (lowest observed effect dose) for toxic thresholds on reproduction and subclinical endpoints. The frequency of liver necrosis and vacuolated hepatocytes increased with increasing Hg concentrations and were significantly highest at the three most contaminated sites. Similar relationships were found for gill lesions. The authors concluded that lesions in sculpin liver and gill tissues were likely to be affected by exposure to toxic

elements. Therefore, sculpins may be suitable monitoring species in future Arctic studies of mining activity and long-range transport of Hg.

Verland et al. (2019) performed a comprehensive study on the histological measures used to investigate Shorthorn sculpins (*Myoxocephalus scorpius*) and Fourhorn sculpins (*Myoxocephalus quadricornis*) at Scoresbysund, East Greenland. The authors linked higher elemental concentrations in liver and gill with increases in hepatic nuclear alterations, interstitial hyperplasia, hypertrophy, inflammation and granulomas, along with gill epithelial hyperplasia, hypertropia, cytoplasmic alterations, lamellar epithelium lifting, and mucus cell hyperplasia (Kaarsholm et al., 2019). Although seemingly not affected by a presence of pollutants in the Nuuk harbor, Dang et al. (2018) has for the first time reported on the presence of endozoic trichodinids in the spleen, kidney and liver of shorthorn sculpin. The study also reported a positive correlation between intensity of endozoic trichodinids in the internal organs and ectozoic trichodinids on the gills. Similarly, in Dang et al. (2019), the presence of pheomelanin pigments in melanomacrophage centers were reported. This is the first time pheomelanin has been shown in shorthorn sculpins, and the second time pheomelanin has been reported in fish at all.

At a former lead-zinc mine in Mestersvig (East Greenland), shorthorns sculpins at the polluted site showed increased prevalence of epithelial hyperplasia, inflammation, intensity of neutral and total mucus cells and chloride cells, along with a decrease in infection of the parasite colonial Peritricha (Dang et al., 2017; Nørregaard et al., 2018). Important differences in histopathology was found between two sculpin species captured there; at the contaminated Nyhavn site, four horn sculpins had a significantly higher prevalence of chondroplastic tissue and intensity of neutral, mixed and total mucus cells in the gills compared to the shorthorn sculpins. This suggests that care should be taken when sampling these two very similar sculpins for purposes of environmental monitoring. The above studies all suggest that lesions in sculpin liver and gill tissues are likely to be affected by exposure to toxic elements.

2.3.6. Other fish taxa

Duffy et al. (1999) reported no relationship between Hg exposure and expression of heat shock proteins (Hsp60, Hsp70) in gills and skeletal muscle for northern pike (*Esox lucius*), burbot (*Lota lota*), whitefish (*Coregonus nelsoni*), grayling (*Thymallus arcticus*), and sheefish (*Stenodus lencichthys*) from the western North American Arctic. Marine fish species Greenland halibut (*Reinhardtius hippoglossoides*), daubed shanny (*Leptoclinus maculatus*), sea tadpole (*Careproctus reinhardti*), Atlantic spiny lumpsucker (*Eumicrotremus spinosus*), polar cod (*Boreogadus saida*), Arctic rockling (*Gaidropsarus argentatus*), doubleline eelpout (*Lycodes eudipleurostictus*), black seasnail (*Paraliparis bathybius*), polar sculpin (*Cottunculus microps*), Atlantic cod (*Gadus morhua*) and capelin (*Mallotus villosus*) collected from reference locations (Faroe Islands, Jan Mayen, Svalbard and the Barents Sea) had concentrations of DNA adducts below or close to the method detection limit (Aas et al., 2003). A similar result was reported by Hylland et al. (2017) for dab (*Limanda limanda*) and haddock (*Melanogrammus aeglefinus*) sampled off Iceland. The latter study also included DNA strand breaks, which were lower in dab collected in Iceland than anywhere in the North Sea. Studies with two of the species (dab, Atlantic cod) in the North Sea or under laboratory conditions have however shown that fish residing in areas with high oil production will accumulate increased concentrations of adducts and/or higher levels of DNA strand breaks (Hylland et al., 2006, 2017; Balk et al., 2011; Holth and Tollefsen, 2012).

3. Challenges and new approaches to assess biological effects

3.1. Contaminant mixtures and multiple stressors

Understanding and predicting the biological effects of complex contaminant mixtures within a multi-stressor framework is one of the great challenges of Arctic ecotoxicology. There are obstacles related to different experimental, modelling and predictive environmental risk assessment approaches. Ongoing environmental risk assessment guidelines and manual developments in Europe aim to incorporate the combined effects of chemical contaminants, the use of different experimental approaches for providing combined effect data, the involvement of biomarkers to characterize modes and mechanisms of action and toxicity pathways, and efforts to identify relevant risk scenarios related to combined effects (Beyer et al., 2014).

For more than a decade, political and scientific communities have requested information that ties together the cumulative effects of multiple stressors (e.g., immune- and endocrine disrupting pollution, infectious disease, climate change, etc.). Since the last AMAP effects report (Letcher et al., 2010), several studies have been published on this, and various hypotheses have been put forward. Polar bears have recently received a considerable amount of focus as a wildlife species impacted by climate change due to the projections of sea-ice loss, and decline in access to their main prey, the ringed seal (Durner et al., 2009; Molnár et al., 2011; Stirling and Derocher, 2012). As a long-lived k-selected top predator species (i.e., large body size, long-living, low population density, few offspring, opportunistic) polar bears may be at greater risk of severe population declines through exposure to endocrine-disrupting chemicals.

3.2. Risk quotient analysis of Arctic wildlife and fish

3.2.1. Methodology

The weight of evidence provided by correlative associations of OHC exposure with various physiological and biochemical endpoints may identify certain contaminant 'hot spots', including East Greenland and Svalbard. However, comprehensive reviews of OHC exposure and effects in Arctic wildlife show there are virtually no data demonstrating a direct OHC-mediated cause-effect (Letcher et al., 2010; Sonne, 2010). To address these concerns, Sonne et al. (2009) employed a RQ approach to investigate the causal linkage between OHC body burdens and reproductive toxicity in an East Greenland polar bear population using an in silico approach to model the additive effects of contaminants. Dietz et al. (2015, 2018) employed this approach to evaluate linkages between OHC exposure and reproductive, immunotoxic and carcinogenic effects in polar bear subpopulations across the Arctic, using the most recent spatial trend data for OHCs (McKinney et al., 2011) and PFOS (AMAP, 2016). RQ calculations were performed based on the ratio of adipose OHC concentrations to estimated critical body residues (CBRs). CBRs were calculated from relatively low critical daily doses determined by laboratory rat studies (0.469 μg/g) using physiologically-based pharmacokinetic (PBPK) modelling (Nielsen et al., 2006; US EPA, 2008). All subpopulations had RQs above the effect threshold, with East Greenland and Alaskan bears showing the highest and lowest risk, respectively. ΣPCBs alone (not including ΣMeSO2-PCBs) accounted for the majority of the risk (95% range: 88–98%).

Here we provide a similar RQ analysis, but expand it to the circumpolar Arctic and for a wide range of marine species. Due to the clear importance of ΣPCBs to the overall risk of effects as reported from previous RQ studies, in this analysis we decided to focus solely on PCBs. As for the critical daily doses, a broad range is available in the literature and the relative sensitivity between species, between regions, or even over time has never been resolved. It was therefore decided to use a more conservative CBR of 10 μg/g lw of PCBs for both effects on the immune system and effects on the hormone system, and hence the type of effects could be depicted in the same graphic (Fig. 5; SI Table 2). This threshold concentration represents the upper range of what was reported as the immune threshold by Desforges et al. (2016) for polar bears, cetaceans and pinnipeds. It is thus likely that the RQs are even higher if the actual critical daily doses are proven to be lower in future studies.

We also include a similar RQ analysis for potential health effects in wildlife as a result of total Hg exposure (see Fig. 6, Table 1 and SI

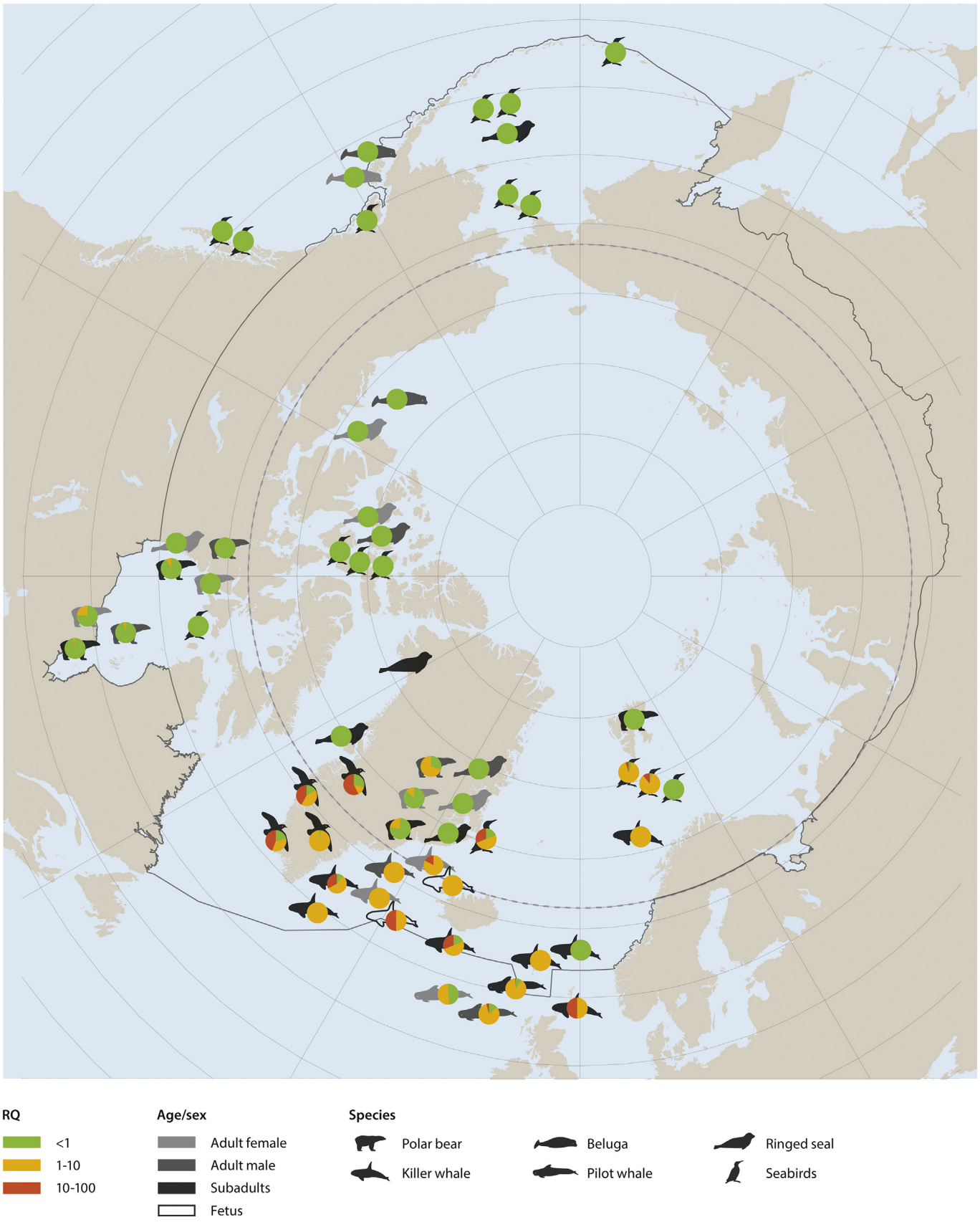


Fig. 5. Risk quotients (RQs) for PCB-mediated effects on the immune and hormone systems based on post-2000 sampling of Arctic key species and their ΣPCB loads using a conservatively determined critical body residue of 10 μg/g lw PCBs. See SI Table 1 for the detailed information upon which this summary graphic is based.

Table 3). This included effects on reproduction and adverse effects on condition, behavior, and productivity. For all species, five risk categories are presently evaluated: no risk, low risk, moderate risk, high risk, and severe risk (Table 1). For marine mammals, hepatic total Hg threshold values were used as identified for harp seal (*Pagophilus groenlandicus*) (Ronald et al., 1977). For terrestrial mammals, hepatic total Hg threshold values were used as determined for mink (*Mustela vison*) (Wobeser et al., 1976; Wren et al., 1987). For birds, the assessment methodology employed by Ackerman et al. (2016) was adapted; this methodology also allowed for the reconstruction of risk categories based on liver concentrations as well as egg concentrations.

3.2.2. Marine mammals

3.2.2.1. Risk for PCB-mediated health effects

3.2.2.1.1. Toothed whales. Available data and calculated RQs for POPs are summarized in Fig. 5 and SI Table 2. Killer whales (*Orcinus orca*) are clearly the most exposed species and all five North Atlantic

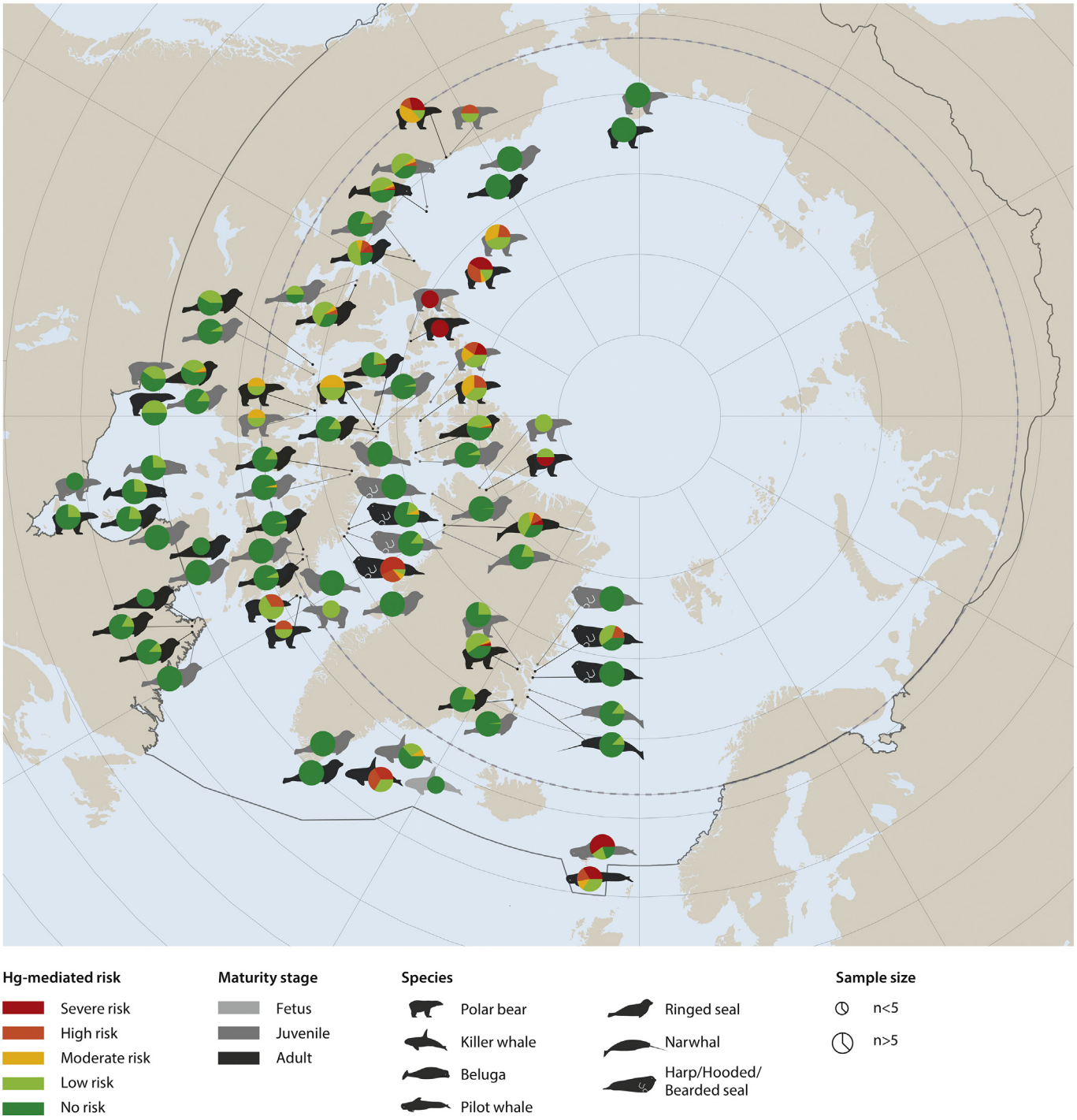


Fig. 6. Geographical overview of the proportion of individuals of specific Arctic marine mammal populations that are at risk of Hg-mediated health effects; based on post-2000 monitoring data grouped according to maturity where possible. The five risk categories are defined using effect threshold categories observed for harp seals (Ronald et al., 1977). See SI Table 2 for the detailed information upon which this summary graphic is based.

Table 1
Estimated risk for health effects in wildlife owing to total mercury exposure. See SI Table 3 for the detailed information underlying this summary table.

	Risk category, μg/g ww				
	No risk	Low risk	Moderate risk	High risk	Severe risk
Marine mammals	<16	16–64	64–83	83–126	>126
Terrestrial mammals	<4.2	4.2–20.5	20.5–26.4	26.4–44.1	>44.1
Birds (blood)	<0.2	0.2–1.0	1–3	3–4	>4
Birds (liver)	<1.4	1.4–7.3	7.3–22.7	22.7–30.5	>30.5
Birds (egg)	<0.11	0.11–0.47	0.47–1.30	1.3–1.7	>1.7

subpopulations studied had animals at risk of PCB-mediated effects on the immune system and hormone system. Between 50% and 100% of the East Greenland, Iceland and Shetland subpopulations fell within the RQ range 1–10, and some (age/sex) categories within three of the five studied North Atlantic subpopulations had 31% to 50% in the RQ range 10–100, indicating a high risk of PCB-mediated effects. However, there were also categories in three of the five subpopulations where 11–100% of animals were not critically affected by PCB exposure (RQ < 1). Pacific killer whales from the coastal waters of central and northern British Columbia, Canada (data not shown due to their distribution outside the Arctic) also had high RQs (Buckman et al., 2011), particularly transient killer whales that consume other marine mammals. All adult transient males fell within the RQ range 10–100 indicating high risk of PCB-mediated effects. The proportion of adult transient females in the RQ range 10–100 was lower (83%) than for adult males (100%). Transient juveniles had lower RQs than adults (all RQs within the range 1–10). Piscivorous northern resident killer whales were found to have RQs 12–23 times lower than those predating on other marine mammals, with none falling within the very high risk category (RQ range 10–100). Between 57% and 91% of animals had RQs of 1 to 10, and 9% to 43% were not affected by PCB exposure (RQ < 1) (Buckman et al., 2011). These findings on the potential for PCB-mediated effects on the immune and endocrine systems of killer whales support previous findings from Jepson et al. (2016) who concluded that highly contaminated killer whale populations at lower latitudes (the UK, Ireland, Canary Islands and Gibraltar) have little to no know reproductive capacity and are at risk of extinction. As well as linking contaminant loads to effect thresholds, Reeves and Notarbartolo di Sciara (2006), Guinet et al. (2007), Beck et al. (2013), Hammond et al. (2013) and Jepson et al. (2016) concluded that only very small killer whale populations now occur in industrialized regions of Europe. Their findings include observations of low numbers, major and long-term population declines, significant contraction of range, lack of observations, low or no reproduction, and strandings.

A population of long-finned pilot whale from the Faroe Islands also had individuals at risk of PCB-mediated effects. Although the majority of adult males (82%) and immature pilot whales (90%) had RQs of between 1 and 10, the RQs for a small percentage of individuals did fall within the highest risk category (10−100); 4% and 1%, respectively. The pattern for adult females was quite different as no individuals fell within the highest risk category (RQs 10–100) and almost half the population (48%) showed no risk of PCB-mediated effects (RQ < 1), with the remaining 52% falling within the intermediate risk category (1−10). This is due to maternal transfer of PCBs to the offspring. The finding that toothed whales other than killer whales can exceed the PCB toxicity thresholds was also reported by Jepson et al. (2016) for striped dolphin (*Stenella coeruleoalba*) and bottlenose dolphin (*Tursiops truncatus*) but not for harbor porpoise (*Phocoena phocoena*). The RQs for beluga were all <1 which indicates that this species is not facing major PCB-mediated effects on immune or endocrine function.

3.2.2.1.2. Polar bears. Although polar bears are on average feeding at a higher marine trophic level than killer whales, their PCB body residues and hence RQs are lower because bears have a much greater ability to eliminate OHCs such as PCBs from their body. In contrast to killer whales, none of the polar bear subpopulations reported here had RQs in the highest PCB- mediated risk category using the conservative CBR of 10 μg/g lw instead of 0.469 μg/g lw as used by Dietz et al. (2015). The majority of bears had RQs < 1, indicating low risk for adverse health effects. The exception was adult males from East Greenland for which 70% of animals showed moderate risk of PCB exposure (having RQs within the range 1–10).

3.2.2.1.3. Seals. All ringed seals and northern fur seals (*Callorhinus ursinus*) had RQs < 1 and thus low risk to potential immune and endocrine effects from PCB exposure.

3.2.2.1.4. Other species. Sonne et al. (2015b, 2016) used a similar approach to evaluate RQs calculated from oral daily doses of PCBs and other OHCs as well as adipose body residues in sledge dogs (*Canis familiaris*) from the controlled feeding study described previously. For both RQ evaluations, the exposed dogs but not the control dogs exceeded immune effect thresholds, corroborating results of in vivo immunotoxicity in the sledge dog cohort studies.

3.2.2.2. Risk for Hg-mediated health effects

3.2.2.2.1. Toothed whales. In general, most marine mammal species are at low risk from total Hg exposure (Fig. 6; SI Fig. 1 and SI Table 3). However, results for some high trophic-level species, such as polar bear, certain toothed whales including pilot whale, narwhal, and beluga, as well as hooded seal, fell outside this broad pattern.

As much as 60% of juvenile pilot whales from the Faroe Islands are at severe risk for total Hg-mediated health effects. For adult pilot whales, 33% of individuals were classified as being at severe risk and an additional 20% at high risk. Because this population was also found to have relatively high loads of PCBs there is a high potential of combined cumulative risk. Risk for total Hg-mediated health effects in adult killer whales is also high, with 33% of individuals at severe risk and 33% at high risk. This contrasts with the situation for killer whale embryos which were all within the no risk group owing to the effective placental barrier for MeHg and total Hg. Juveniles were all within the three lowest risk categories: moderate risk (9%), low risk (27%) and no risk (64%). However, it is unclear whether toothed whales can cope with higher total Hg loads than harp seals, which have been used to categorize the risk thresholds. Adult narwhal from the Qaanaaq region were also shown to be at risk, with 7% of individuals from this population at severe risk and 13% at high risk, which was not the case for narwhal on the Greenland East Coast around Ittoqqortoormiit for which there were no individuals in either risk category. For adult beluga from Hendrickson Island, 1% of individuals are considered to be at severe risk and 3% at high risk. A higher percentage of juveniles from this population are at high risk (5%), but none are at severe risk.

3.2.2.2.2. Seals. Adult hooded seals from Davis Strait in the Canadian eastern Arctic had the second highest number of individuals with a total Hg exposure of severe (57%) and high (29%) risk. Around Ittoqqortoormiit, on the Greenland east coast, the exposure of hooded seal (all age classes) seemed to be lower with only 20% of the population at high risk and none at severe risk. Adult harp seals from the Davis Strait had even lower exposure with 7% of individuals at moderate risk and none at high or severe risk, while the juvenile harp and hooded seals were at low or no risk. Three of the 33 ringed seal groups had individuals in the severe risk category: adult seals from Sachs Harbor (11%), Resolute (2%) and Arviat (1%). Six of the 33 ringed seal groups had individuals in the high risk category: adult seals from Sachs Harbor (11%), Resolute (1%), Arviat (1%), Ulukhaktok (6%) and Grise Fjord (3%), as well as juveniles from Sachs Harbor (2%). All of these populations were in the northeastern to central Canadian high north in exactly the

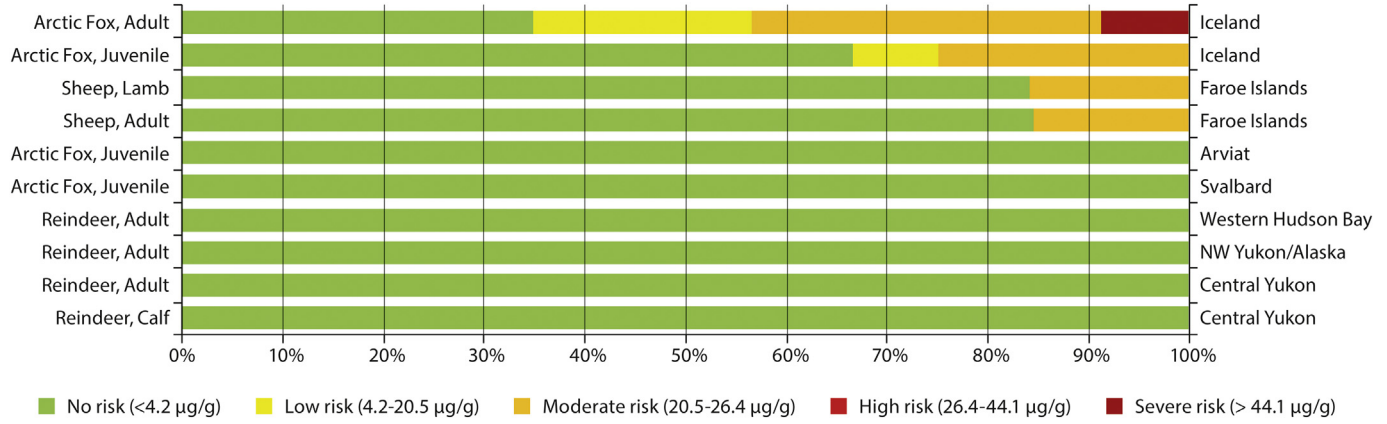


Fig. 7. Ranked overview (from highest to lowest risk) of the proportion of individuals, where possible grouped according to maturity, of specific Arctic terrestrial mammal populations that are at risk of total Hg-mediated health effects. Following 2000–2015 hepatic concentrations, five risk categories are reported based upon effect threshold categories observed for mink (Wobeser et al., 1976; Wren et al., 1987).

same area that had the highest Hg concentrations in polar bears. These areas have previously been identified as high Hg risk areas (Dietz et al., 1998, 2013c). Bearded seals (*Erignathus barbatus*) seemed to be at no risk from total Hg exposure as the majority of individuals were exposed to levels that are thought not to be associated with any risk.

3.2.2.2.3. Polar bears. Adult polar bears from the northern Beaufort Sea were the third highest total Hg exposure group with 41% of the population at severe risk, and 35% at high risk of Hg-mediated health effects. The other polar bear populations at severe risk were juvenile bears from Qaanaaq (33%), adults from the southern Beaufort Sea (29%), juveniles from Lancaster/Jones Sound (20%), and adults from Ittoqqortoormiit (3%). All these populations have a substantial percentage (2–35%) at high risk. In addition, some polar bear populations had data from a few individuals that show alarmingly high exposure, such as adult bears ranging up to 414 µg/g ww from the northern Beaufort Sea. Other polar bear groups with low sample size ($n < 8$), such as juveniles from the Gulf of Boothia and adults from the southern Beaufort Sea, showed exposure associated with high risk of effects.

The molar ratio of Hg:Se has been found to be 1:1 in tissues of marine mammals with high Hg exposure, suggesting that Hg and Se can be bound in complexes (Koeman et al., 1973, 1975; Dietz et al., 2000). So if the molar ratio of Hg:Se is >1 this may indicate a Se deficiency for binding to and thus detoxifying tissue Hg, or that the essential nutrient Se has been scavenged. On the other hand, Hg:Se complex may also be highly reactive, and depletion of Se pools has been suggested to be driving mechanism for neurotoxic effects for marine mammals (Gajdosechova et al., 2016). The molar ratio of Hg:Se was reported by Routti et al. (2011) for polar bears harvested during the period 2005–2008 from ten circumpolar subpopulations. The molar ratio of Hg:Se was found to be ~1.5 for bears from the Gulf of Boothia and East Greenland, but also above one in the southern and northern Beaufort Sea, southern Hudson Bay, and Lancaster/Jones Sound subpopulations. For Hudson Bay polar bears, annual monitoring from 2006 to 2015 of total Hg in liver shows total Hg concentrations have remained essentially unchanged, ranging between 10 and 15 µg/g ww over this period (Letcher and Dyck, 2016). Thus, Hudson Bay polar bears can be considered at low risk. Nevertheless, the findings for the Canadian Arctic and East Greenland polar bears highlight the severity of the total Hg exposure issue in polar bears.

3.2.3. Terrestrial mammals

3.2.3.1. Risk for PCB-mediated health effects. PCBs concentrations have been analyzed in 141 arctic foxes from Svalbard, and it was found that these foxes forage in terrestrial as well as marine ecosystems and that the POP concentrations observed originated from the marine diet (Andersen et al., 2015). However, as no PCB raw data were available for these foxes or other terrestrial mammals we were not able to calculate RQs for terrestrial biota. In addition, reindeer diet of the foxes was related to negative HCB concentrations and that HCH concentrations were related to sea ice cover. In summary, the diet of foxes was related to climate fluctuations and thereby exposure to various POPs (Andersen et al., 2015).

3.2.3.2. Risk for Hg-mediated health effects. The majority of Hg RQs in terrestrial mammals fell within the two lowest risk categories for total Hg-mediated health effects (no risk and low risk, see Fig. 7). For sheep on the Faroe Islands, 15% are at moderate risk, which could be attributed to agricultural fertilization by fish remains or eutrophication by bird droppings (from the extensive seabird colonies on the islands). Caribou/reindeer (*Rangifer tarandus*), and even Hudson Bay and Svalbard Arctic fox seem not to be at risk. Icelandic Arctic fox, however, had low to moderate risk for 8–35% for its population of juveniles and adults, with 9% of the adult population being at severe risk.

3.2.4. Marine birds

3.2.4.1. Risk for PCB-mediated health effects. For the majority of seabirds, PCB data were only available for eggs and blood, resulting in less accurate RQs. Concentrations of PCBs in seabird eggs from Alaska, Canada, East Greenland and Norway (Bjørnøya) all translated into RQs < 1, indicating little risk of PCB-mediated effects on the immune or endocrine systems. In contrast, based on PCBs in blood, glaucous gulls from Bjørnøya had much higher risk of PCB-mediated effects with most birds having RQs that fell within the moderate risk category (90% of females, 85% of males). Relatively few birds had RQs within the highest (5% of females, 11% of males) or lowest risk group (<1) (5% of females, 4% of males).

3.2.4.2. Risk for Hg-mediated health effects. In contrast to PCB loads, which were highest in the eastern Arctic, the highest total Hg concentrations were found in Alaska, with intermediate concentrations in Canada and the lowest concentrations in the North Atlantic region (Fig. 8; SI Fig. 2 and SI Table 3). Concentrations in three species of adult birds from western North America showed populations of northern fulmar, double-crested cormorant (*Phalacrocorax auritus*) and pigeon guillemot (*Cepphus columba*) to be at severe risk (4–15%) or high risk (3–26%). In addition, eggs from ivory gull (*Pagophila eburnea*) at Cape Kluyw (14%), thick-billed murre (*Uria lomvia*) at Prince Leopold Island (4%) and black guillemot (*Cepphus grylle*) from the Faroe Islands (1%) were

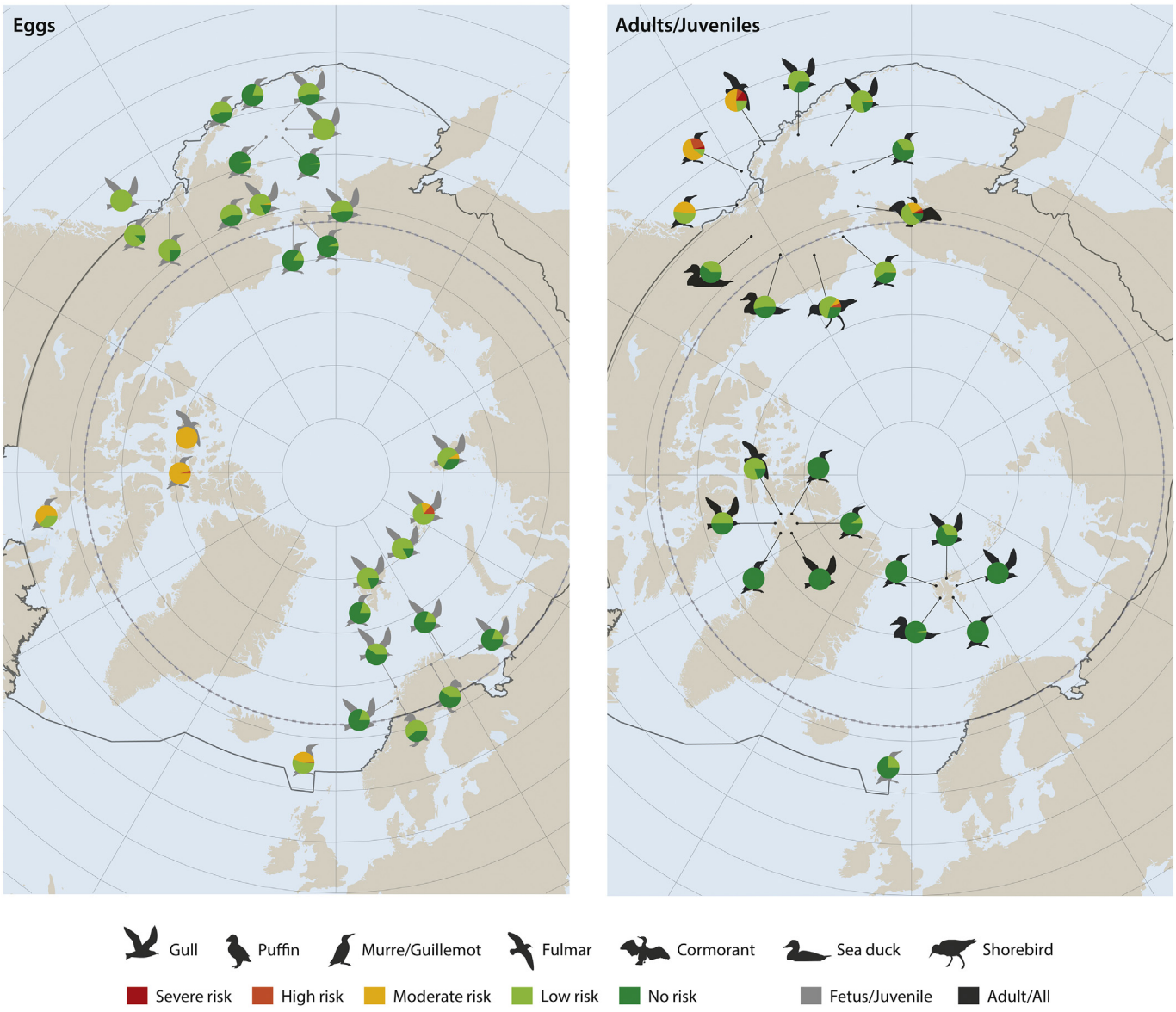


Fig. 8. Geographical overview of the proportion of individuals of specific Arctic marine bird populations that are at risk of total-Hg mediated health effects; based on post-2000 monitoring data grouped according to maturity where possible. Results based on bird egg monitoring data and results from monitoring of adult/juvenile birds. The five risk categories are defined using effect threshold categories for North American bird species (Ackerman et al., 2016). See SI Table 3 for details of datasets, sources and effects category thresholds.

found to be at high risk. The remaining species were not found to be at risk or were at low risk (Fig. 8; SI Fig. 2 and SI Table 3).

3.2.5. Terrestrial birds

3.2.5.1. Risk for PCB-mediated health effects. PCBPCB levels in birds of prey were determined in liver tissue. White-tailed eagles from West Greenland were used where adipose correction factors allowed for harmonization as a result of comparisons of multiple tissues. The three birds of prey studied on Greenland (white-tailed eagle, gyrfalcon *Falco rusticolus* and peregrine falcon *F. peregrinus*) showed high risk of PCB-mediated effects. The proportion of animals within the highest risk category varied from 38% to 57%, with slightly lower proportions (14% to 38%) in the moderate risk range. Only 15% to 29% of individuals in each population showed no risk of PCB exposure (RQ < 1). In contrast, snowy owl (*Bubo scandiacus*) had PCB concentrations that were 10–20 times lower and so had much lower RQs. At 83%, the proportion of birds that were not affected by PCB exposure (RQ < 1) was also much higher.

3.2.5.2. Risk for Hg-mediated health effects. The northern shoveler (*Anas clypeata*) from western North America was the terrestrial bird species with the highest risk for total Hg-mediated health effects, with 14% of individuals at severe risk, 5% at high risk, 29% at moderate risk, 35% at low risk, and only 17% at no risk (Fig. 9; SI Fig. 3; SI Table 2). Other terrestrial bird species at severe risk included adult common loon (*Gavia immer*; 5%), peregrine falcon (4%), Pacific loon (*G. pacifica*; 3%), red-throated loon (*G. stellate*; 3%), bald eagle (*Haliaeetus leucocephalus*; 2%), green-winged teal (*A. carolinensis*; 2%), and yellow-billed loon (*G. adamsii*; 1%). Adult greater scaup (*Aythya marila*, 2%) from western North America was found to be at high risk. Moderate risk was observed for white-tailed eagle from Swedish Lapland (17%), adult red-necked grebe (*Podiceps grisegena*; 14%), juvenile gyrfalcon from Nuuk on the west coast of Greenland (8%), and adult osprey (*Pandion haliaetus*) from western North America (2%). In the moderate risk group, almost all bird groupings were represented and the five highest were adult common loon (35%), peregrine falcon (29%), northern shoveler (29%), bald eagle (26%) and greater scaup (21%), all from western North America.

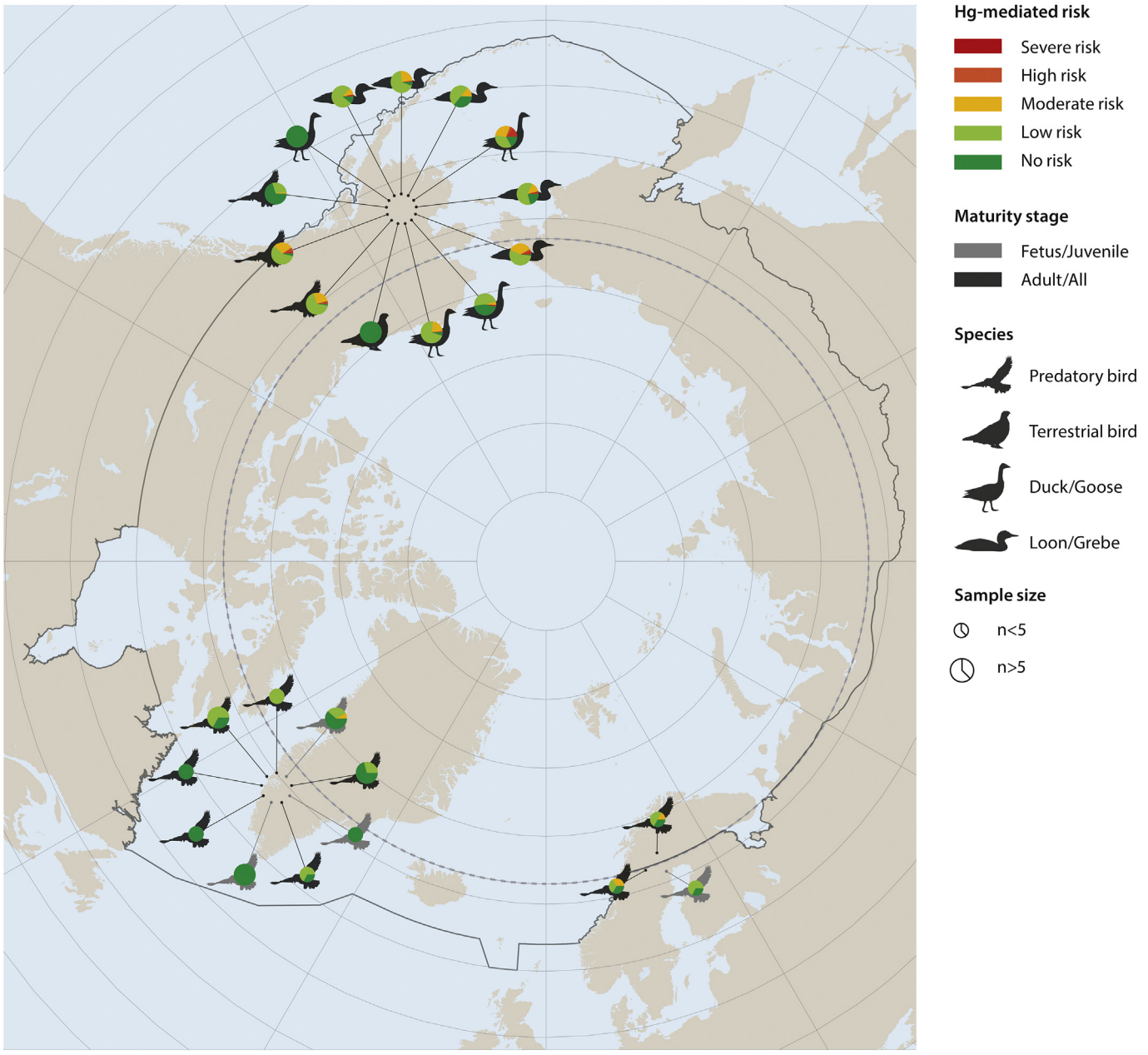


Fig. 9. Geographical overview of the proportion of individuals of specific Arctic terrestrial and freshwater bird populations that are at risk of total-Hg mediated health effects; based on post-2000 monitoring data grouped according to maturity when possible. The five risk categories are defined using effect threshold categories for North American bird species (Ackerman et al., 2016). See SI Table 2 for details of datasets, sources and effects category thresholds.

3.3. What is a "normal physiological range?

The normal range, or reference intervals, for important physiological endpoints in Arctic terrestrial and marine species are poorly characterized. Examples of endpoints include serum biochemistry, hematology, hormone and cytokine values, functional immune assays, and body condition. Statistically-derived reference intervals provide a baseline against which individual test results can be compared, thus allowing an evaluation of individual health relative to a 'normal' healthy population. Reference values are typically reported as upper and lower bounds of a reference interval comprising 95% of a healthy population. To date and in regards to Arctic species, reference intervals have been established for serum chemistry values for free-ranging beluga, harp seal, and ringed seal (Nordoy and Thoresen, 2002; Tryland et al., 2006a, 2006b), as well as for managed-care beluga (Norman et al., 2013).

There are several challenges in developing reference intervals for free-ranging Arctic species. The main challenge is obtaining an adequate sample size to establish a reference interval for a particular biomarker. Procedures for establishing reference intervals based on reference sample size and distribution have been recommended by the American Society for Veterinary Clinical Pathology for wildlife species, with sample sizes ranging from 20 to 120 (Friedrichs et al., 2012). Other considerations include the tissue/sample to collect (e.g., blood/serum/plasma, urine), time to collection (e.g., fresh/live capture versus stranded versus fresh dead), tissue storage (e.g., room temperature, −20 °C, −80 °C, liquid nitrogen), central tissue bank/repository, and permits to ship samples internationally (i.e., endangered/protected species) to a

laboratory with the equipment to analyze the sample. Most important are the validation and usefulness of the biomarkers and reference intervals as tools to help make the link between contaminant exposure and adverse health outcomes in individuals and populations.

Sonne et al. (2008) used reference intervals to investigate the impacts of OHCs on the health of Arctic top predators using domestic Greenland sledge dogs as a model for East Greenland polar bears. Two urine and 29 different blood plasma parameters were measured and compared to established reference interval values for canines. Overall, the use of reference intervals allowed for the detection of differences in kidney and liver chemistry values between exposed and control dogs. The authors suggested that their data shows that a number of clinical blood parameters are potential biomarkers of OHC exposure in wildlife.

3.4. Case studies of multiple stressors in the Arctic

3.4.1. Climate change

A literature review by McKinney et al. (2015) gave initial insights into the ecological aspects of climate change-contaminant interactions. Other studies have suggested ecological change without actually collecting such corroborating data. In remote and aquatic environments it can be very difficult to directly assess ecosystem change, particularly for species and their trophic relationships (Bowen and Iverson, 2013). This may be improved by using ecological tracers, among which are bulk tissue stable isotope ratios and fatty acid profiles. The associated analyses are inexpensive relative to contaminant analyses and can often be achieved with little or no additional sample collection or requirements. Ecological tracer data paired with contaminant exposure data can increase understanding of the ecological changes altering contaminant pathways within species, populations or food webs. An example of this approach is provided by McKinney et al. (2013) who investigated how climate change may have affected the long-term (1984–2011) feeding ecology and contaminant exposure of East Greenland polar bears. Dietary analysis using quantitative fatty acid concentrations revealed that changes in the distribution and availability of ice-dependent seals had resulted in higher OHC concentrations in the polar bears due to a prey-shift from ringed seals to hooded and harp seals. Developing and refining additional tissue-derived tracers of habitat use and trophic interactions (e.g., compound-specific isotope analysis; McKinney et al., 2013) together with other ecological information (e.g., lipid content as a body condition metric; McKinney et al., 2014) may be useful for improving understanding of changing contaminant levels and pathways, and their associated health effects.

As an iconic Arctic species, polar bears have been the focus of many studies on the effects of climate change on animal health. Based on recent temporal studies on plasma biomarkers for starvation in eastern Beaufort Sea polar bears, it has been suggested that a greater proportion of bears now fast (Cherry et al., 2009). Increased fasting is likely to be due to broad-scale changes in Arctic sea ice composition owing to climate change and the consequent impact this has on prey availability (Cherry et al., 2009). Body condition indices of Hudson Bay polar bears also support evidence of increased starvation due to reduced access to ice-associated seals (Molnár et al., 2011). Furthermore, qualitative and/or quantitative changes in diet and reduced body condition (i.e., adipose stores) of polar bears can affect their tissue concentrations of lipophilic pollutants. A recent study by Tartu et al. (2017b) examined Svalbard polar bears and considered how variations in adipose stores, associated with both breeding status and spatial and seasonal changes in sea-ice conditions, and diet influence concentrations and biotransformation of POPs. Body condition was found to be negatively related to sea-ice extent at both temporal and spatial scales, and relative to diet, it was the most important predictor for concentrations of POPs in plasma and fat. The authors concluded that declining sea ice indirectly leads to increased concentrations of lipophilic pollutants in (Svalbard) polar bears mediated through reduced feeding opportunities and declining body condition rather than changes in dietary composition. Furthermore, fatter females were more efficient at biotransforming PCBs than leaner females (Tartu et al., 2017b). The size of the polar bear subpopulations of Hudson Bay has decreased by approximately 22% and it has been proposed that this could be due to reduced body condition index and lowered sub-adult survival (Stirling et al., 1999; Obbard et al., 2006; Regehr et al., 2007). Because of the southern distribution of the Hudson Bay subpopulation, these polar bears may serve as a proxy for future climate change impacts on their circumpolar health and survival. For example, the consequence of energetic stress combined with the physiological effects caused by the bioaccumulation of chemical contaminants could prove significant for the distinct East Greenland subpopulation since that carries some of the highest loads of endocrine-disrupting chemicals in the Arctic (Sonne, 2010).

Jenssen et al. (2015) reviewed available literature on the combined effects of climatic change and exposure to POPs in polar bears and concluded that one of the greatest threats was reduced access to seals due to loss of sea ice, resulting in prolonged fasting periods which would in turn affect body condition (emaciation), survival and reproductive success. Catabolic processing of peripheral adipose tissue, in order to compensate for the lower energy intake, is likely to increase blood concentrations of toxic and bioavailable contaminants and metabolites that will exacerbate harmful impacts on various organ systems. Poor body condition is also likely to induce metabolic changes with negative impacts on hormones, blood chemistry homeostasis, survival rates and fecundity (Sonne, 2010). For instance, Chow et al. (2011) found that fasting bears reduce amino acid- and protein catabolism by limiting cortisol bioavailability through the elevation of serum cortisol-binding-globulin. Nevertheless, studies focusing on climate change, POP interactions and their effects on wildlife and humans still remain to be conducted on a larger scale, to generate results that would further clarify these relationships.

Decreasing their consumption of seals may lower polar bear OHC exposure, but may also have indirect consequences such as decreasing crucial vitamin intake. Lower seal consumption could also lead to more bear-bear and bear-human interactions and time on land, which makes them more susceptible to wounding, hunting by humans and drowning (Monnett and Gleason, 2006). Ultimately, these factors increase bear mortality and reduce their total circumpolar number, although the survival of each subpopulation will depend on the specific sea-ice reductions in each particular habitat. For example, the most pronounced polar bear habitat loss since 2000 has occurred around East Greenland and Svalbard, and in the same period polar bear body size has decreased in both subpopulations probably due to a combination of energetic stress and neuroendocrine disruption (Sonne, 2010). Ecotourism (e.g., at Svalbard), oil exploration/exploitation, anthropogenic underwater noise, increased and changing shipping routes including the possibility of traverse through the North-West and North-East passages, and an influx of new species are likely to be additional co-factors in the combined stressors to polar bears.

3.4.2. Infectious diseases and zoonoses

Novel and shifting of wildlife disease patterns in the Arctic are of increasing interest (Shope, 1991; Burek et al., 2008). As well as novel distributions of various disease pathogens, this interest covers significant changes in prevalence, increasing pathogen-survivability and changes in morbidity/mortality. A novel distribution is largely driven by climate change and specifically Arctic warming, which has seen a northward influx to the Arctic of new wildlife and insect species as vectors for disease, as well as accelerated pathogen lifecycles. Kutz (2009) reported that the lifecycle of the muskoxen (*Ovibos moschatus*) lungworm (*Umingmakstrongylus pallikuukensis*) had shifted from a two-year cycle to a one-year cycle, and that its distribution had recently shifted several hundred kilometers northward to populations previously regarded as devoid of the parasite (Kutz et al., 2013; Solomon, 2014). Similarly, the nematode *Setaria tundrae* has migrated northward in Finland

infecting previously unaffected reindeer following consecutive warm summers (Ball et al., 2001). Another example is the moose tick (*Dermacentor albipictus*) which has been spreading northward in the Northwest Territories, Canada. Ticks are arthropods, and arthropods generally hold great potential as disease vectors for both animals and humans (Sonenshine and Mather, 1994; Kutz, 2009). Because arthropods are sensitive to temperature (Elias, 1994), higher temperatures are likely to increase the abundance of disease-carrying arthropod vectors. As in the Northwest Territories of Canada, ticks have also been observed to be moving northward in Sweden (Lindgren and Gustafson, 2001). Human cases of tick-borne encephalitis increased 50-fold between 1980 and 2009 in the northern Russian province of Arkhangelsk Oblast (Solomon, 2014). Extreme weather events linked to climate change have also been tied to outbreaks of zoonotic disease (Ahern et al., 2005). This is thought to be mediated through rodent vectors being expelled from their burrows by flooding, sewage contaminated waterways, and prime conditions for waterborne disease pathogens such as *Cryptosporidium*, *Vibrio cholera*, *Escherichia coli*, *Salmonella* and *Giardia* as well as for mosquito breeding grounds that are left behind after floods (Epstein, 1999; Palmieri et al., 2012).

Fish-borne zoonoses such as *Anisakis simplex*, *Diphyllobothrium latum*, *Contracaecum osculatum* and *Pseudoterranove decipiens*, carried by typical fish for human consumption, are also expected to gain better lifecycle conditions in warmer waters. Climate associated changes include accelerated embryonation and hatching of eggs in seawater as well as accelerated development of larval stages, increased numbers of crustacean intermediate hosts and a northward movement of paratenic and final hosts (Rokicki, 2009; Scholz, 2009). Many of these pathogens have already been found in high prevalence in Greenland cod (*Gadus ogac*) and Atlantic cod (*G. morhua*) as well as Greenland halibut (*Reinhardtius hippoglossoides*; Mouritsen et al., 2010; Karpiej et al., 2013).

Few studies have examined the incidence of zoonotic transmitted diseases in humans in the Arctic. The majority of such studies have been performed in Alaska and Canada, with just a small number of studies in Greenland and Russia. This is despite a significant proportion of the indigenous Arctic residents living in close contact with wildlife. Indeed, traditional food preparation often avoids heat treatment. This process can be extremely ineffective against zoonotic diseases as shown by the case of *Toxoplasma gondii* (which causes life-long parasitic cysts in the human brain): 80% of Inuit consuming dried marine mammal meat tested seropositive for the disease, while prevalence was only 10% in Cree who prefer cooked meat (Messier, 2008). Andersen-Ranberg (pers. comm.) undertook a comprehensive review of zoonotic diseases present in key Arctic wildlife species. This showed that at least 26 zoonotic pathogens occur in a wide range of species that are typically hunted throughout the Arctic. It is clear that zoonoses are a very real threat to Arctic residents, and this highlights the need for an overview of the most serious zoonotic diseases, especially for those Arctic regions where information is particularly sparse. The need for an overview is strengthened by the context of changing disease patterns, as well as ongoing bioaccumulation and exposure to toxic chemical contaminants, some of which have been proven to be immune-suppressive. This would render both animal and human hosts more vulnerable to diseases, especially hosts that are already immunologically vulnerable to novel diseases (Dietz et al., 1989; Ross et al., 1995; Sweet and Zelikoff, 2001; Sonne et al., 2006a; Corsini et al., 2014; Bogomolni et al., 2016).

Antibiotic resistant bacteria have also been found in the Arctic. This signals that antimicrobial resistance is now spreading worldwide (Sjölund et al., 2008) and highlights the need for more knowledge-based diagnostics and treatment concerning pathogens actually infecting people in the Arctic. Weber et al. (2013) proposed that species in the Arctic have adapted to life in harsh climatic conditions that limit pathogen density and this has resulted in conditioned immune defenses to lower pathogen loads. Their proposal was based on the results of a study on major histocompatibility complex (MHC) genes, essential for immune function, which showed low variance in the MHC binding site in Canadian polar bears. This would theoretically mean that because the variance of the MHC binding sites is low, it can detect fewer infecting pathogens than if the variance was high. If this is true, it puts polar bears and perhaps other Arctic resident wildlife species under further constraints in terms of the effects of multiple stressors.

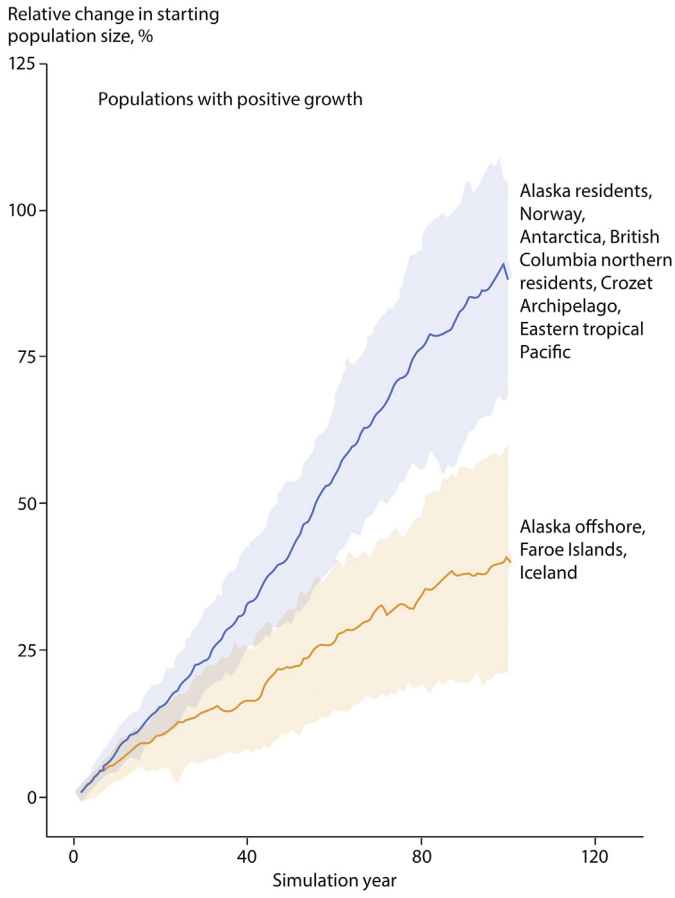
3.5. Population modelling and omics

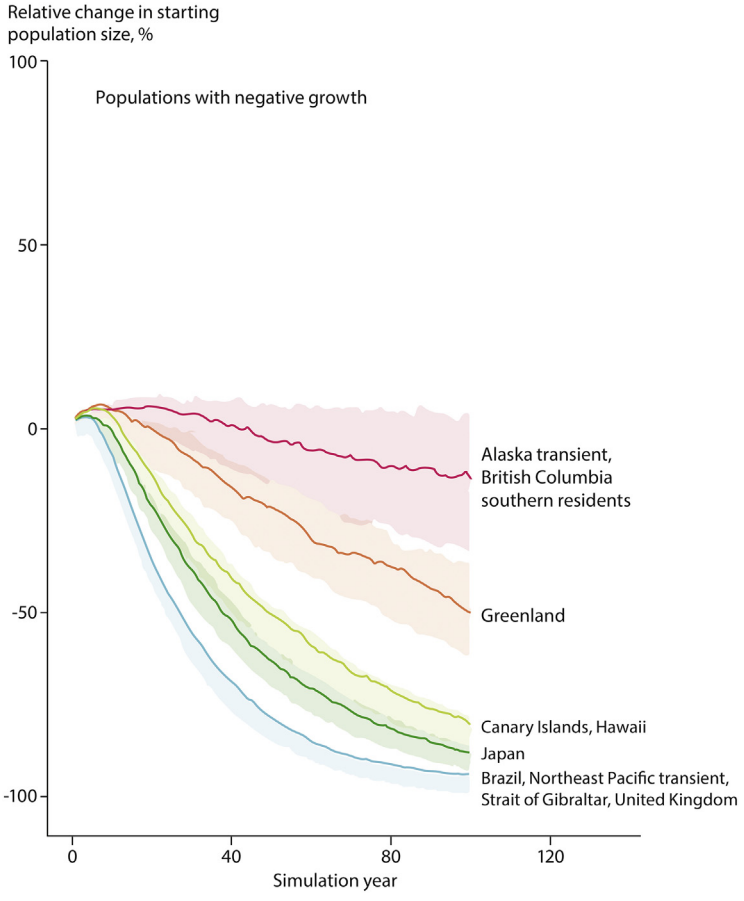
3.5.1. Population modelling

Most toxicological studies, including those reviewed in this effects assessment, apply a traditional risk assessment approach whereby biological/physiological effects are measured at the individual level, be it on the molecular, cellular or organ scale. In contrast, environmental protection goals within regulatory and conservation bodies are most interested in impacts at the population level. Owing to obvious logistical, financial and ethical restrictions, it is effectively impossible to conduct exposure experiments on whole populations. Thus, effects on individuals can be used as proxies and extrapolated to the population scale. Despite the importance of this exercise, few studies have attempted to evaluate the effects of POPs and Hg on wildlife populations, especially in the Arctic; this is likely to be related to knowledge gaps in wildlife population metrics and mathematical modelling challenges.

Ecological modelling, particularly individual-based models, has increased in popularity for extrapolating effects at the individual level to the population level (Martin et al., 2013). These individual-based models can incorporate physiologically relevant parameters on each individual within a population, which is particularly important for ecotoxicology where exposure and risk of effects changes throughout life-history (e.g., reproductive transfer, growth, bioenergetics, diet). Pavlova et al. (2016a) used an individual-based model to evaluate the population-level consequences of PCB exposure and effects on female reproduction in East-Greenland polar bears. This study was a crucial step forward in extrapolating individual reproductive effects from laboratory experiments on mink as a surrogate species, to population responses in a polar bear population shown to be vulnerable to effects on various biomarkers of health (see this and previous AMAP assessments e.g. Letcher et al., 2010). Although a low risk for reduced population growth was found in the original mink-based toxicity model, the authors showed that slightly more potent dose-response curves for polar bear cub mortality (EC50 < 18 ppm lw) would result in significant population declines (Pavlova et al., 2016a). Modelling approaches such as this are essential for testing hypotheses and predicting population responses to various exposure/toxicity scenarios. Furthermore, PBPK modelling can be instrumental in the development of bioaccumulation models that feed into larger population-effect assessments. Bioaccumulation models have already been developed for many marine mammals, including beluga, pilot whale, harbor porpoise and ringed seal (Hickie et al., 2000, 2005; Weijs et al., 2012, 2014). These models are currently used to compare body burdens with established toxicity thresholds, providing useful measures of the proportions of populations at risk of adverse effects. However, future models could incorporate PBPK bioaccumulation into more elaborate individual-based models or other population-level models of toxic effects.

A recent study by Desforges et al. (2018) used an individual-based model framework combining PCB effects on calf survival and disease mortality to determine population effect predictions of PCBs on killer whale populations around the world. Killer whales are one of the most highly PCB-contaminated species on Earth, raising questions regarding consequences for individuals and at the population level (Jepson et al., 2016). Desforges et al. (2018) showed that PCB-mediated effects on reproduction and immunity can have potentially severe consequences for the long-term population viability of 10 of the 19 killer whale populations with measured PCB tissue burdens. The majority of the Arctic killer whale population were not predicted


Relative change in starting population size, %
125
100
75
50
25
0
Populations with positive growth
Alaska residents, Norway, Antarctica, British Columbia northern residents, Crozet Archipelago, Eastern tropical Pacific
Alaska offshore, Faroe Islands, Iceland
0
40
80
120
Simulation year


Relative change in starting population size, %
100
50
0
-50
-100
Populations with negative growth
Alaska transient, British Columbia southern residents
Greenland
Canary Islands, Hawaii
Japan
Brazil, Northeast Pacific transient, Strait of Gibraltar, United Kingdom
0
40
80
120
Simulation year

to decline (northern Norway, Faroe Islands and Iceland) but the East Greenland killer whales eating marine mammals showed potential risk of population decline (Fig. 10).Their results highlight the vulnerability of killer whale populations to the persistent threat of PCBs, and provide an important step forward in efforts to extrapolate and understand contaminant effects at the population-level.

Traditional approaches to risk assessment and combined stressors are typically descriptive in nature, and while these can explain patterns in collected data and allow statistical analyses of interactions, they provide no information on the underlying processes causing the effects. Furthermore, descriptive methods cannot easily be extrapolated to conditions outside those tested, meaning they cannot inform about new stressors, time-dependent effects, new combinations of stressors, or effects on different endpoints (Jager et al., 2010). It is not feasible to test every exposure scenario given the infinite combination of possible contaminant mixtures combined with other natural and anthropogenic stressors. Biology-based, or process-based, approaches are therefore necessary to describe the physiological mechanisms that underpin the effects of stressors in animals.

Bioenergetics models can be useful in this context as these provide a framework to explain animal metabolic organization and mechanistically link stressors to physiological modes of action (Kooijman and Bedaux, 1996). Mechanistic models, such as dynamic energy budget models, therefore explain the impact of stressors through the alteration of energy-costly metabolic processes which are fundamentally linked in an organism via changes in energy allocation. In this way, multiple stressors can be compared on a similar basis (i.e., energy) and predictions can be extrapolated to combined effects.

Regardless of modelling methods used, further knowledge is required on species-specific dose responses for various health endpoints that can be related to population impacts, such as reproduction, fertility and mortality. More challenging and just as interesting, is the need to develop innovative models that can measure impacts of morbidity. The majority of biomarkers described in this assessment indeed influence morbidity, more so than direct mortality/reproduction. The consequences of endocrine or immune dysfunction are difficult to model at the population level because these parameters have not yet been directly linked to demographic parameters which are used in traditional population-matrix models. Here process-based energy budgets can provide exciting opportunities to quantify these often ignored morbidity effects of pollutants by means of energetic trade-offs between important physiological systems. Although most dynamic energy budget models currently focus on lower trophic organisms due to the ease of their study, models do exist for polar bears and North Atlantic right whales (*Eubalaena glacialis*).

The polar bear model has been used to estimate the impact of climate change on bear survival and reproduction as well as measuring the Allee effect (Molnár et al., 2010, 2011, 2014). The right whale dynamic energy budget model incorporates PBPK modelling and bioenergetics to predict individual growth, reproduction, bioaccumulation, and transfer of energy and contaminants from mothers to their young (Klanjscek et al., 2007). Although these are not population-effect models for contaminant exposure, they illustrate how morbidity can affect physiological functions, and indirectly influence population growth. A recent systematic literature review by Bechshøft et al. (2018) investigated the ecological and physiological variables that have been integrated in early POP studies on polar bears and more recent toxicology-based studies, where a total of 207 research papers were published between 1970 and 2016. The frequency with which ecological and physiological variables were integrated into toxicological papers varied. Among the highlights were that age and (or) sex was the only ecological variable(s) considered in 51% of papers. A total of 37% of the papers investigated physiological effects in relation to contaminant concentrations. A total of 98% dealt with contaminant exposure at the individual level, thus leaving population level effects largely unstudied. From these findings, it was suggested that future polar bear toxicology studies need to increase sample sizes, include more ecological variables, increase studies on family groups, and increase the applicability of studies to management and conservation by examining pollution effects on reproduction and survival.

3.5.2. New "omics" based techniques

The past five years or so have seen advances in approaches and techniques for assessing toxicology and biological effects and different levels of biological organization. As reviewed by Bahamonde et al. (2016), a major area of advancement has been the 'omics' revolution, which has generated unprecedented amounts of data on molecular changes that occur in a cell, tissue, or whole organism. For ecotoxicology, these approaches have been used to annotate adverse outcome pathways for environmental contaminants, to characterize chemical modes of action, to investigate mechanisms of organismal adaptation, and to identify candidate biomarkers of exposure and effect. There are numerous examples of studies applying 'omics' technologies to study environmental contaminants, and these have most often included gene transcription analysis and more recently next-generation sequencing (Jefferies et al., 2012; Wiseman et al., 2013).

Furthermore, proteomic and metabolomic studies are becoming more prevalent, as they can address post-transcriptional changes associated with contaminant exposure. A new and promising field of research termed exposomics has the daunting task of combining 'omics' approaches in order to study cumulative environmental exposures and associated biological responses throughout life (Dennis and Jones, 2016). This study of the exposome is based on the understanding that health and disease are influenced not only by genetics but also by environmental factors, such as chemical exposure.

There only appears to be two published studies that have reported on the use of 'omics' approaches in Arctic wildlife and fish and in relation to POP or OHC exposure. In a first report for any Arctic species or population, Tartu et al. (2017a) investigated polar bear plasma metabolome and lipodome in relation to OHC exposure as a part of a larger study on contaminant effects on lipid metabolism in female polar bears from Svalbard (see also Section 2.1.8). The authors used a non-target approach and only the most important metabolites or lipids that were affected by environmental or physiological factors were quantified. Multivariate analyses showed that plasma metabolome and lipidome, based on 111 and 101 samples, respectively, clustered according to season (April, September). Glucose and lactate were the main metabolites driving the seasonal segregation with higher concentrations in feeding (April) compared to fasting (September) individuals, and they were decreased with increasing plasma PFAS concentrations. Furthermore, concentrations of a lipid, glycerophosphocholine 37:3, was negatively related to lipophilic POPs, suggesting that the synthesis of this lipid may be affected by POPs. Morris et al. (2018) recently reported on the measurement and profiling of low molecular weight endogenous metabolites (metabolomics) that reflect the dynamic response of biological systems to stress factors. A targeted, quantitative metabolomics platform (219 metabolites including amino acids, biogenic amines, acylcarnitines, phosphatidylcholines, sphingomyelins, hexoses and fatty acids), was evaluated in muscle and liver of polar bears from representative southern and western Hudson Bay (Canada) subpopulations (SHB and WHB, respectively). Five metabolites discriminated the hepatic profiles of SHB males and females (hexose, arginine, glutamine, one phosphatidylcholine, one sphingomyelin), while the 15 discriminatory metabolites contrasting the livers of males

Fig. 10. Combined reproductive and immune effects of PCBs on population size of killer whales simulated for a 100-year period. Bold line and shading represent the median and interquartile range represented as a percentage of starting population size. Panels are divided by populations with positive growth and negative growth.
Modified from Desforges et al. (2018).

from SHB and WHB were primarily phosphatidylcholines, along with leucine. It was concluded that the unique metabolite profiles discriminating the sexes, and particularly those discriminating the subpopulations, may have utility for future assessments of the effects of stressors (including contaminant exposure) on the physiological state of Hudson Bay polar bears and those from other subpopulations. In a follow-up study, Morris et al. (2019) used these metabolomics profiles in combination with POPs and total Hg data, and applied multivariate statistics to assess differential influences on the hepatic metabolome of male polar bears from the SHB and WHB. *Per*- and polyfluoroalkyl substances (PFASs), PBDEs, *p,p′*-DDE and some highly chlorinated *ortho*-PCB congeners were greater in the SHB bears, and inversely correlated with the discriminating metabolites in the liver. Significant elevation of symmetric dimethylarginine (SDMA) in WHB bears, where concentrations of legacy OCPs were greater, suggested differences in renal function. The arachidonic acid, glycerophospholipid and amino acid pathways were identified as impacted. Elevated levels of arachidonic acid in the SHB could be related to differences in chronic exposure to hepatotoxic contaminants, since arachidonic acid accompanies the inflammation response. Overall, the results suggested linkages between elements of the hepatic metabolome and differential contaminant exposure in Hudson Bay polar bears.

The goals of 'omics' technologies in field-based ecotoxicology are to develop monitoring tools for regulatory purposes. Data from various 'omics' approaches as well as from other levels of biological integration, are increasingly integrated and part of Adverse Outcome Pathways (AOP) frameworks. AOP frameworks inherently attempt to provide some estimated extrapolation to individual or ideally population level outcomes (Kramer et al., 2011). In AOP frameworks, molecular initiating events precede adverse cell and tissue responses, and are therefore more sensitive than higher level apical endpoints, in theory allowing for earlier detection of potential adverse effects. Although controlled laboratory experimental conditions determine 'omics' responses under various environmental stressors, identifying these responses in natural populations is essential for understanding the cumulative effects of multiple environmental stressors (both chemical and natural) under field conditions, and the relevance of the changes in intact ecosystems.

The recent emphasis on determining 'omics' responses in wild populations generates new perspectives on the impacts of contaminants in complex environments, but also detracts from the ability to link cause and effect as a result of these same uncontrolled and poorly defined environmental conditions. Fent and Sumpter (2011) and Hook (2010) recently reviewed the advantages and limitations of omics in ecotoxicology. There was a consensus that although high-throughput analyses offer unsurpassed data generation, there are significant challenges related to reproducibility, variability, and interpretation, especially in non-model species for which few molecular datasets exist. There are necessary steps to move omics from proof-of-concept to a more functional and useful tool that can then be applied to regulatory or traditional environmental monitoring approaches. Thus, researchers are already aware that studies addressing basic modifying factors in the field (i.e., impact of variables such as season, sex, species, and nutritional status on normal biological variation) are required before further discussions regarding the use of 'omics' technologies in environmental regulation and monitoring can proceed.

4. Synthesis and knowledge gaps

4.1. New information since the previous AMAP assessment

In terms of POPs, effects studies on wildlife and fish have largely focused on legacy OHCs and in particular on summed levels for different classes of chemical (∑PCBs, ∑DDTs, ∑CHLs, ∑HCHs), rather than individual compounds or congeners. More recently, ∑PBDEs and ∑PFASs have received increasing attention, although information on the latter is almost completely focused on perfluoroalkyl acids (PFAAs) and specifically on the highly bioaccumulative PFOS.

Common among all Arctic wildlife and fish studies since 2010 is that a number of different groups of biomarker and/or effect endpoints have been consistently measured in wildlife: hormones (steroid and thyroid), vitamins (especially vitamins A and E), immune system activation (antibodies or cell proliferation), and liver enzyme activity (CYP-450), in correlative relation to contaminant levels in tissues or body compartments (blood or plasma). Histopathology has also been studied for some species. As summarized in Supplemental Information Table 1, the increase or decrease in levels and expression of these biomarker endpoints in association with levels of PCB and/or Hg varies across phyla, species, populations and regions.

CYP-450 enzyme activity is reported to have increased with OHC concentrations across all studies since 2010. In contrast, concentrations of hormones and vitamins generally showed negative associations with OHCs, although this varied depending on species and tissue/body compartment. The immune system was also negatively correlated with OHC levels across species, and this included both the humoral and cellular systems. Novel biomarkers of reactive oxygen species and genotoxicity have recently been employed in a few species of mammals and birds. Histopathological changes have been shown to occur in liver, kidney and thyroid glands and seem to be affected negatively by OHC and Hg concentrations; this is also the case for bone mineral density. Interpretation of these effects on the population level, however, remains a challenge. New studies on polar bear brains have shown steroid hormones to be positively correlated with PFAS levels, while neurochemical endpoints were negatively correlated with levels of the same PFAS compounds. Polar bear, pilot whale, beluga and glaucous gull are the four species analyzed for a broader range of biomarkers. Across these species, thyroid hormones generally decreased while vitamins A and E increased in liver and decreased in blood. Concentrations of steroid hormones did not show a clear association with OHCs, although there was a tendency for testosterone to be negatively correlated with PCB levels. Of the recently applied biomarkers, genotoxicity has been shown for polar bears and for a few birds and fish species, and mainly driven by PCB exposures. Several studies using different approaches suggest that also energy metabolism is affected by pollutant exposure in polar bears and several bird species.

Specific effects associated with (combined) contaminant exposure have been reported in several Arctic wildlife species and populations. Based on PCB concentrations being the dominant effect contributor, a conservative PCB critical body residue (CBR) of 10 μg/g lw has been used to calculate RQs for a number of species in the Arctic region and bordering sea areas, and where sufficient published data were available. Killer whales were found to be the marine mammal species most at risk, with a large proportion of individuals in all five study populations having an RQ above 1, and thus implying risk of PCB-mediated health effects. This is also the case for transient Pacific killer whales just south of the Arctic region. Long-finned pilot whales from the Faroe Islands also had large group proportions with RQs above 1. In contrast, beluga and ringed seals from all circumpolar populations studied all seem to have RQs below 1, indicating that the immune and hormonal systems of these Arctic species are unlikely to be detrimentally affected by PCB exposure. Several populations of birds of prey, however, do seem to be at risk of PCB-mediated biological health effects: White-tailed eagle (*Haliaeetus albicilla*), gyrfalcon (*Falco rusticolus*) and peregrine falcon all had a large proportion of individuals with RQs above 1.

In general, based on the most recently published information, most marine mammal species are at no or low risk for health effects mediated by Hg exposure. However, for some species at high marine trophic levels, such as polar bear, pilot whale, narwhal and beluga, as well as hooded seal, a proportion of the population is at high or severe risk for health effects mediated by Hg exposure. Polar bears from the central Canadian High Arctic and Alaska, as well as pilot whales from the Faroe Islands, carried the hepatic total Hg burdens of greatest concern.

Bird Hg concentrations were above toxicity benchmarks in many areas of the marine environment. This was particularly the case for seabirds, including northern fulmar (*Fulmarus glacialis*), double-crested cormorant (*Phalacrocorax auritus*) and pigeon guillemot (*Cepphus columba*). Freshwater and terrestrial species in the Alaskan environment including northern shoveler (*Anas clypeata*), common loon (*Gavia immer*), peregrine falcon, red-throated loon (*G. stellate*), Pacific loon (*G. pacifica*), bald eagle (*Haliaeetus leucocephalus*), green- winged teal (*A. carolinensis*) and yellow-billed loon (*G. adamsii*) also exhibited Hg concentrations above effect thresholds. In the North Atlantic, only a small proportion of unhatched chicks of black guillemot (*Cepphus grylle*) were at high risk of Hg exposure. As expected, terrestrial mammals, with the exception of Arctic foxes (*Vulpes lagopus*) on Iceland, which showed low to moderate risk, did not show risk for Hg intoxication, based on the limited recent Hg data available. There is a lack of Hg data for many Arctic species and regions, including the Russian Arctic. In addition, in some studies, the number of individuals of a given species obtained was not sufficient to allow conclusions to be drawn regarding the proportions of the population falling within a given health risk category.

4.2. Knowledge gaps and suggested improvements

New information from effects studies on Arctic species has resulted in important new insights into the risks for biological effects on Arctic wildlife from exposure to environmental contaminants. However, major knowledge gaps remain with regard to the biological and toxicological effects of OHCs, Hg and, in particular, contaminants of emerging Arctic concern that are now being reported in Arctic biota. These knowledge gaps include concentration thresholds for biologically relevant health effects and toxic threshold endpoints used to develop RQs. Integrating wildlife and human health assessments has the potential to improve knowledge regarding the combined effects of contaminant exposure and natural stressors (e.g., infectious and zoonotic diseases), and how multiple stressors are directly and indirectly influenced in a changing Arctic, especially in connection with climate change. There is a need for new methods and approaches, including the expansion of in vitro experimental approaches, studies on the individual, and combined effects of single compounds and chemical mixtures. Increased use of in silico modelling is needed to better predict biological effects at the population and ecosystem level. Specific knowledge gaps and information deficiencies are as follows.

Improving future monitoring programs

- Certain Arctic regions, such as Russia, Fennoscandia and Alaska, are not adequately represented in the monitoring of wildlife and fish exposure and effects, despite relevant studies in the Russian Arctic in particular having been called for in all previous AMAP assessments since 1998 (AMAP, 1998; Dietz et al., 1998; AMAP, 2004; Letcher et al., 2010; AMAP, 2011; Outridge & Dietz et al., 2011).
- Greater attention needs to be given to access to data on hunting quotas and takes for relevant species.
- There are a number of invasive and migratory wildlife and fish species, including killer whale and capelin (*Mallotus villosus*), which are not represented or are under-represented in Arctic monitoring and research addressing biotic changes due to the changing Arctic climate.
- Further pan-Arctic harmonization is required in relation to target species, sampling frequency and season, and methods applied for the measurement of contaminants and associated biomarkers and biological endpoints that are applicable to effects assessment. In doing so, there is a need for increased communication and collaboration with local and indigenous people.

Improving effect assessments

- Effects need to be assessed within a changing Arctic and multi-stressor framework.
- To better inform policy, projections regarding future OHC- and Hg-elicited effects on wildlife and fish populations could be improved using growing data compilations on OHC and Hg exposure levels and trends, and in relation to observed climate change-related variables (e.g., sea ice loss). This information would be incorporated within, for example, scenario assessments performed by AMAP and those summarized by the Intergovernmental Panel on Climate Change.
- There is an ongoing need to establish and refine concentration thresholds for biologically relevant health effects in (Arctic) wildlife and fish. Such studies are often expensive so international collaboration is encouraged.
- Physical-chemical and industrial production data are required for newer chemicals of emerging Arctic concern.

Multidisciplinary studies

- Effects need to be assessed in relation to spatial and temporal variation in dietary pathways of exposure. There is also a need to assess the combined effects of contaminant exposure and natural stressors.
- The 'One Health' concept, if explored in future assessments integrating information from wildlife and human health studies, is expected to help provide novel insights.
- There is a need for better identification of cumulative and interactive effects thresholds of contaminant exposure.

Specific possible improvements and future directions for this new area of global climate change-linked ecotoxicology, include (i) routine analysis of ancillary ecological metrics together with OHC and Hg studies, (ii) simultaneous consideration of the multiple mechanisms by which global climate change and contaminant interactions can occur, (iii) targeted research on species known to be sensitive to both global climate change and contaminants, and (iv) studies linking these changes to changes in major impact parameters such as immune and reproductive function and development, particularly at the population level. Moving forward, environmental chemists studying contaminant levels in biotic and abiotic media, eco(toxico)logists and indigenous peoples of the Arctic could have greater impact by working together to consider the combined impacts of these changes on contaminant exposures in Arctic marine and terrestrial biota.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Support was provided for participants in the core group of the AMAP Assessment by the DANCEA (Danish Cooperation for Environment in the Arctic) program for employees at Aarhus University while support for Canadian participants was received from the Northern Contaminants Program (NCP; Indigenous and Northern Affairs Canada (INAC)), Environment and Climate Change Canada (ECCC), Chemicals Management Plan (CMP; ECCC and Health Canada), Department of Fisheries and Oceans (DFO) Canada and the Natural Sciences and Engineering Research Council of Canada. Funding sources for the large number of additional writing, data and sample contributors are likewise acknowledged. We gratefully acknowledge the reviewers including those that peer-reviewed the AMAP Effects Assessment, which is the basis of the present journal review including the U.S. Geological Survey (USGS) and National Institute of Standards and Technology, Editorial Review Board (NIST ERB). Likewise, numerous people including

colleagues and Inuit hunters in various circumpolar jurisdictions assisted with sample collections, analytical work and age determination for the many published studies as well as any new data that was used. The following persons provided comments, data or samples but did not find their contribution important enough to justify a co-authorship: Ingeborg Hallanger, Lisa Bjørnsdatter Helgason, Audrey Jæger, Heli Routti and Filipa Samarra. The USGS acknowledges any the use of trade, product, or firm names in the publication is for descriptive purposes only and does not imply endorsement by the U.S. Government. J.T. Ackerman and C. Eagles-Smith were supported by the USGS Environmental Health Mission Area's Contaminant Biology Program.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.133792.

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